Review Article

Wake-Promoting Agents, Insights into Clinical Use and Molecular Perspectives

Bijan Zare[1], Behrooz Moosavi[2,3], Mohammad Torabi-Nami[4,5*]

[1]Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, China
[3]Laboratory of Organometallics, Catalysis and Ordered Materials, State Key Laboratory of Advanced Technology for Materials Synthesis and Processing, Wuhan University of Technology, Wuhan, China
[4]Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
[5]Shiraz Neuroscience Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

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Abstract

Wake-Promoting Agents (WPAs) such as amphetamine-like stimulants or modafinil, armodafinil, methyl phenidate, caffeine and nicotine reinforce the level of vigilance through an stimulated release of neurotransmitters implicated in the arousal threshold maintenance, hence shift the drive from the sleep-promoting to wake-promoting system. The modulatory effects of WPAs on cortical activation pathways give rise to enhanced vigilance. For example, cholinergic neurons of the basal forebrain and the adenosine receptors on these neurons are agonized and antagonized by nicotine and caffeine, respectively. Caffeine similarly antagonizes adenosine receptors on the GABAergic neurons and intensifies the inhibitory drive in preoptic/anterior hypothalamus which involve in sleep induction. Modafinil however exerts its wake-promoting effects through stimulating the tuberomammillary nucleus and the hypocretinergic neurons which activate the ascending reticular activating system. Although many neurotransmitter systems such as dopamine are thought to be involved upon the effects of WPAs, the empirical evidence to explain the exact mechanisms need to gain strength.

The Burden of Excessive Daytime Sleepiness

Sleepiness is in fact resulted from the less-maintained arousal threshold which relieves the inhibition exerted on the sleep-promoting system upon wakefulness. Daytime somnolence, characterized by inability to keep awake and vigilant during the typical waking hours of the day, can turn into persistent drowsiness or unintended sleep. Moreover, sleepiness may significantly vary in intensity and tend to occur in situations which require minimal or no active participation (1).

The practice of general medicine encounters frequent cases with sleep-related complaints including excessive daytime sleepiness (EDS). EDS is shown to leave strongly negative effects on individuals' quality of life, mood, interpersonal communications, and functionality. Despite such a significance, EDS is often under-diagnosed in clinical practice. While EDS is known to significantly interfere with patients' health and functional status, surveys have revealed that almost in 60% of

instances, the primary physicians do not track this in patients (2, 3).

Clinically, when subjects obtain the score of 10 and more in a self-rated questionnaire known as Epworth Sleepiness Scale (ESS), they will be regarded as cases of EDS. On the other hand, the Psychomotor Vigilance Task (PVT) or steer clear test are utilized as objective assessments of sustained vigilant attention in the practice of sleep medicine in cases who present with the complaint of excessive sleepiness. Some more comprehensive sleep laboratory-based tests to confirm the diagnosis of EDS include multiple-sleep latency test (MSLT) and maintenance of wakefulness test (MWT) (4-8).

When EDS is a chronic condition secondary to continued sleep deprivation (intense shift work, for instance) and especially when subjects are critical job holders who need to deal with sensitive vehicles, catastrophic accidents may occur. Whatever the cause of EDS might be, drowsy driving is known to result in many traffic road accidents and this has lately turned to be among the foremost health priorities in many countries (9-12).

EDS may result from numerous sleep-related insufficiencies and long-lasting disorders including obstructive or central sleep apnea/hypopnea syndrome, circadian rhythm disorder and shift work, chronic insomnia, parasomnias, restless-leg syndrome, drug effects, narcolepsy, idiopathic hypersomnia (with or without long sleep time) and several related medical disorders. These conditions not only potentially give rise to EDS but also affect cardiovascular, neurological and psychiatric status of the sufferers (13-15).

In general, EDS may present in various qualities. For instance, narcolepsy and idiopathic hypersomnia may both represent EDS, however unlike narcolepsy which is characterized by sleep attacks and propensity to fall sleep during the day, idiopathic hypersomnia with long sleep time is mainly described by sleep inertia or inability to terminate sleep(16-18).

With regard to the prevalence of EDS, overall standardized prevalence is shown to range from 10-15% of general population in different studies. However, EDS is more prevalent among older-age strata with almost involving 35% of the subjects over the age of 80 (19-27).

The management of EDS largely depends of targeting and overcoming the underlying cause of sleep inefficiency and related disorders. However, in the event of unexplained EDS, wake-promoting agents (WPAs) are prescribed and expected to assist patient's performance. Howbeit, these agents have always had a true potential of abuse (28).

WPAs such as amphetamine-like stimulants or modafinil, armodafinil, methylphenidate, caffeine and nicotine reinforce the level of vigilance through an stimulated release of neurotransmitters implicated in the arousal threshold maintenance, hence shift the drive from the sleep-promoting to wake-promoting system. The modulatory effects of WPAs on cortical activation pathways give rise to enhanced vigilance. For example, cholinergic neurons of the basal forebrain and the adenosine receptors on these neurons are agonized and antagonized by nicotine and caffeine, respectively. Caffeine similarly antagonizes adenosine receptors on the GABAergic neurons and intensifies the inhibitory drive in preoptic/anterior hypothalamus which involve in sleep induction.

Modafinil however exerts its wake-promoting effects through stimulating the tuberomammillary nucleus and the hypocretinergic neurons which activate the ascending reticular activating system. Although many neurotransmitter systems such as dopamine are thought to be involved upon the effects of WPAs, the empirical evidence to explain the exact mechanisms remain thin (28-35). Understanding how wake-promoting drugs interact with different components of the dopamine system to induce arousal remains a challenge for future research to establish new stimulant treatments (31).

This paper provides an overview on different drugs used as WPAs.

Wake Promoting Agents (WPAs)

Problems of 'wakefulness', including states of impaired alertness, vigilance and attention affect millions of individuals (36). Several drugs belong to different chemical classes are used as wake-promoting medications. Direct-acting sympathomimetics (e.g. phenylephrine), indirect-acting sympathomimetics (e.g., methylphenidate, amphetamine), and non-sympathomimetic stimulants (e.g. caffeine, modafinil and armodafinil) are pharmacologic interventions to treat excessive sleepiness. Hypothalamic neuropeptide (hypocretin or orexin) are recently reported to have an important role in the regulation of sleep and arousal states (37, 38).

Some well-known untoward effects of psycho-stimulants including increased feelings of anxiety and agitation, erectile dysfunction, insomnia, decreased libido, and in some cases, mania are reported. Below, the main drugs used as wake promoting agents are reviewed.

- *Modafinil*

Modafinil, holds the chemical name, molecular formula and the molecular weight 2-[(diphenylmethyl) sulfinyl] acetamide, $C_{15}H_{15}NO_2S$ and 273.35 g/mol, respectively. It is a white to off-white, crystalline powder, practically insoluble in water and cyclohexane while sparingly to slightly soluble in methanol and acetone.

Modafinil is shown to improve the activity of wake-promoting neurons through increasing dopamine extracellular concentration partly through the blockade of dopamine transporters (39-41). While many studies have predetermined its possible action on dopamine, adrenalin, noradrenalin, serotonin and GABA systems, the precise mechanism of action of modafinil has remained unclear (41, 42). Although the dopaminergic and norepinephrinergic systems appear to be crucial targets for modafinil action, they seem not to be exclusive and modafinil's mechanism of action is found to be far more complex. According to earlier reports, modafinil directly or indirectly modulates several neurotransmitters other than catecholamine such as histamine and orexin (43). As reported in a double-blind placebo-controlled trials, 200–400 mg per day modafinil significantly reduced sleepiness, hence the medication is recommended as a first-line therapy for sleepiness (44, 45).

Modafinil with an elimination half-life of 13.8 hours is a long-acting compound. Its maximum concentration is achieved in 2–4 hours after intake. Generally, response to modafinil depends on the catechol-O-methyltransferase genotype (46). The drug is initially prescribed at 100 mg twice daily for 1–2 weeks and then increased to 200 mg twice daily. Most common adverse events are mild and comprise headache (13%), nervousness (8%) and nausea (5%), with no evidence of tolerance and low potential for abuse. Modafinil can raise hepatic cytochrome P450 enzyme concentrations and increase the metabolism of different drugs such as oral contraceptives (47, 48).

A systematic review and meta-analysis of the efficacy of modafinil in narcolepsy has proposed significant benefits of modafinil for the treatment of EDS as assessed by ESS (ESS declined by 2.73 points), multiple sleep latency test (MSLT prolonged by 1.11 min) and MWT(MWT increased by 2.82 min) (48, 49). Modafinil appears to lack the similar addiction potential of other dopamine transporter (DAT) inhibitors, such as amphetamine, methylphenidate and cocaine. Modafinil is also shown to reduce the excessive sleepiness observed in patients with shift work disorder (SWD) and results in a notably improved performance. Shift workers with EDS underwent treatment with 200 mg of modafinil or placebo before the start of each shift with their symptoms studied for 3 months (50). Although modafinil reduced lapses of attention in tests, it resulted in no loss in daytime sleepiness as compared to placebo (51).

A review of several aspects of modafinil, focusing on its use for ES in patients with SWD, narcolepsy and residual sleepiness in the syndrome of obstructive sleep apnea is published by Schwartz (51). Generally with modafinil treatment, there was an objective reduction in sleepiness and improvement in general clinical conditions related to the severity of sleepiness. The improvement in wakefulness was associated with an improvement in both behavioral alertness and functional status as well as in health and quality of life. In patients with SWD, there were decreases in the maximum level of sleepiness during night work, in the level of sleepiness during the travel to home and in the incidence of accidents. Modafinil as a drug was well-tolerated with no impairment in sleep or cardiovascular parameters. Long-term studies suggest that the efficacy is maintained with little likelihood of tolerance and there were no adverse effects on scheduled sleep, demonstrating the beneficial effect of modafinil on daily-life and well-being (51).

- *Armodafinil*

The R-enantiomer of modafinil known as armodafinil, has recently been approved to treat excessive sleepiness associated with OSA, SWD, and narcolepsy. Armodafinil has a longer half-life and is approved for the treatment of ES associated with SWD in some countries. Armodafinil has been shown to improve alertness and performance (52).

Armodafinil is used similarly in the treatment of EDS associated with the narcoleptic syndrome, obstructive sleep apnea, and shift-work sleep disorder. Plasma concentration following armodafinil administration lasts longer than that following modafinil administration, resulting in a more prolonged effect during the day and potential improvement in sleepiness in the late afternoon in patients with narcolepsy. A single dose of 150 or 250 mg armodafinil is given orally in the morning for treatment of the narcoleptic syndrome or obstructive sleep apnea and a single dose (150 mg) is prescribed 1 hour before starting work for the management of shift-work sleep disorder. Reduced doses are recommended in the elderly and in patients with severe hepatic impairment (52, 53).

- *Amphetamines*

Stimulants include naturally occurring substances such as cocaine and caffeine or synthetic drugs for example amphetamine and dexamphetamine, methamphetamine, pemoline, bupropion, ephedrine/pseudoephedrine and methylphenidate broadly acting as both dopaminergic and noradrenergic reuptake inhibitors at varying degrees (54).

Amphetamines including L-amphetamine, D-amphetamine and methamphetamine were coined from amphetamine that was initially synthesized as 1-methyl-2-phenethylamine and initially used to treat narcolepsy (55, 56).

Amphetamine was initially synthesized in Berlin in 1887 as 1-methyl-2-phenethylamine (55). Amphetamines have been used for narcolepsy since the 1930s (53). At low doses, the main effect of amphetamine is to release dopamine and to a lesser degree, norepinephrine through reverse efflux via monoamine, dopamine and norepinephrine transporters. At higher doses, monoaminergic depletion and inhibition of reuptake occurs. Similar to modafinil, amphetamines are racemic compounds with their D-isomers more potent on dopamine transmission than L-isomers and subsequently have a greater stimulating effect (57).

The methylated form of amphetamine named methamphetamine exerts a potent wake-promoting effect because it more efficiently crosses the blood brain barrier.

Beside the effectiveness of amphetamines in reducing sleepiness, they showed adverse effects including disturbances of mood and behavior in addition to cardiac and gastrointestinal effects. The most common drug related effects are loss of appetite, insomnia, emotional labiality, nervousness, fever, irritability and impulsivity and at worst, psychotic reactions. On the other hand, insomnia, hypertension and abnormal movements can also occur at large doses (60 mg/day and beyond) (53, 55).

Amphetamine is effective at the dose of 10- 60 mg/day. The therapeutic effects begin within 45−60 min after ingestion of an immediate-release tablet, with peak effect in 2 to 3 hours, and a total duration of 4−6 h. Effects peak about 4−7 h after ingestion of extended-release doses, and last about 12 h, depending on the dose (57).

- *Methylphenidate*

Methylphenidate, another N-methyl derivative of amphetamine, with a shorter half-life, milder side effects, and low abuse potential has been used since 1970 instead of amphetamine (58). It is a potent stimulant that primarily acts by blocking of the reuptake of monoamines (mainly dopamine) and, unlike amphetamines, does not inhibit the vesicular monoamine transporter. It improves daytime sleepiness in patients with narcolepsy at daily doses of 10–60 mg, going up to 100 mg daily at most for severe cases (59).

The effect of methylphenidate is thought be similar to effect of amphetamines. However, there is an argue for a slight superiority of amphetamines. Adverse effects of methylphenidate are similar to amphetamines adverse effect, but to a lesser degree. Methylphenidate probably has a better therapeutic index than D-amphetamine and showed less reduction of appetite or increase in blood pressure. Methylphenidate with relatively short duration of action (3–4 h) supposed to be useful in cases that needs to maximum alertness or at a specific time of day (59, 60).

- *Gamma hydroxybutyrate*

Gamma-hydroxybutyrate (GHB) (sodium oxybate®) is a short-chain fatty acid derivative of gamma-aminobutyric acid (GABA). This compound readily crosses the blood-brain barrier to enter the central nervous system (57, 61). It is a $GABA_B$ receptor agonist at a pharmacological doseand leaves a positive effect on EDS. Gamma-hydroxybutyrate, is approved by the EMA for the treatment of narcolepsy and by the US FDA for the treatment of cataplexy and EDS in patients with narcolepsy (58, 59). The frequency of inadvertent daytime naps and night-time awakenings reduced with GABA (58). However, common side effects of gamma aminobutyrate are dizziness, headache, nausea, pain, somnolence, sleep disorder, confusion, infection, vomiting, and enuresis (58).The major problem with GHB is its non-medical use. GHB is misused in athletes for its metabolic effects (growth hormone-releasing effects). However, post marketing follow-up studies indicate that abuse potential in patients with narcolepsy receiving sodium oxybate is low (59, 61). Overall, gamma hydroxybutyrate is effective, and recommended for treatment of cataplexy, EDS, and disrupted sleep due to narcolepsy (58).

- *Orexin (Hypocretin)*

The neuropeptides orexin produced in hypothalamic neurons also known as hypocretin. In this system two neuropeptide was recognized orexin A and orexin B. Recently, the critical role of orexin system in regulation of arousal and maintenance of wakefulness as well as other behavioral traits such

as feeding and reward processes have been proven in several studies.

On the other hand, orexin deficiency is seen in narcolepsy in humans, suggesting that the orexin system is particularly important for maintenance of wakefulness.

Orexin stimulates waking active monoaminergic and cholinergic neurons in the hypothalamus and brainstem regions to maintain a long, consolidated waking period. Also orexin system effects complex interactions between monoaminergic/cholinergic wake–promoting and GABAergic sleep–promoting neuronal systems.

Research for the orexin agonist and antagonist for the treatment of sleep disorders has forcefully increased over the past decades. As a result, this system may be a potentially important therapeutic target for the treatment of sleep disorders, and orexin replacement therapy would probably be an alternative promising strategy for both sleepiness and cataplexy (62-64).

Since a drug should be delivered to the site of action to show its effect, orexin with peptide structure encounter blood brain barriers as an obstacle. It is the main reason for defeat in peripherally and systemically administration approach. Intra-cerebro-ventricular route for orexin administration is possibly the most effective, but unsuitable for the treatment of patients. Other noninvasive method such as intranasal delivery that targets drugs to the brain along olfactory and trigeminal neural pathways, bypassing the BBB and minimizing systemic exposure and side effects (62).

Orexin-producing cell transplantation might theoretically provide a cure for patients with narcolepsy. Recent improvements in stem cell technology open a new insight to overcome the problems of cell therapy approach such as graft rejection, low survival rate of implant and lack of supply for graft availability (57).

- *Thyrotropin-releasing hormone*

Thyrotropin-releasing hormone (TRH) and its agonists have alerting properties and could help in improving the waking system. TRH at high doses and TRH agonists increase alertness and have been showed to be wake-promoting and anti-cataplectic in the canine narcoleptic model.

However, older clinical trials, mainly on depression, reported little efficacy on mood and on alerting effects (57,59).

- *Caffeine/paraxanthine*

Caffeine is a widely an earliest used stimulant and often used in the treatment against daytime sleepiness and narcolepsy (59). Caffeine as a natural alkaloid, rapidly absorbed through the gastrointestinal tract. It is primarily metabolized in the liver, by demethylation, to 1,7-dimethylxanthine via cytochrome P-450 1A2. The variable effect of caffeine within a population may be explained by differing cytochrome P450 activities between individuals (56). Because of low potency of wake-promoting effect of caffeine high dose is need to reach the best effect, where cardiovascular side effect is the bottleneck (58, 59). However, caffeine is known as an adenosine A1 and A2a receptor antagonist. Zhi-Li et al used knockout mouse to show that caffeine-related increase in wakefulness depends on adenosine A2a receptors (65). Paraxanthine, is a metabolite of caffeine with greater stimulant properties and longer-lasting wake promoting potency, lower toxicity and lesser anxiogenic effects (56, 59).

Pitolisant

Pitolisant is a histamine H3 inverse agonist which has passed phase-III clinical trials for the treatment of EDS and narcolepsy. Histamine H3 receptors reduce the synthesis and release of histamine (66). In a double-blind randomized trial, Dauvilliers et al. showed that pitolisant at doses up to 40 mg was efficacious on EDS compared with placebo and well-tolerated compared with modafinil. They suggested that pitolisant could offer a new treatment option for patients with narcolepsy and EDS (67).

- *Other wake-promoting drugs*

Mazindol, an imidazole derivative, has similar pharmacological effects to the amphetamines. However, it is a weak releasing agent for dopamine, it also blocks dopamine and adrenaline reuptake with high affinity and holds some efficacy on sleepiness. Adverse events are frequent, including weight-loss, dry mouth, nervousness, constipation and, less frequently, nausea, vomiting, headache, dizziness and tachycardia. A careful cardiology follow-up is recommended. Mazindol has less potential for abuse and tolerance than amphetamines (57).

The challenges of studying wakefulness at molecular level

Studying arousal has been facing several challenges including involvement of various neural circuits and neurotransmitter systems. Sometimes arousal-inducing drugs may not be specific for a particular target resulting in other effects. Additionally, target proteins might be distributed

throughout the brain raising the question "whether all the targets required for the drug effect to be observed?" Understanding the wakefulness and sleep phenomena at molecular level in eukaryotes such as zebra fish, fruit fly, and mouse can solve at least some of the issues raised. Conservation of sleep genetics and pharmacology, simplicity of the organism and the control which can be posed over the interfering factors has provided the opportunity to decipher molecular events occurring during wakefulness and sleep. This particularly has advanced as a result of development of molecular biology tools such as conditional knockout technology, virus-mediated gene transfer and RNAi technology using the model organisms (66).

Pharmacogenetics of sleep-wake therapeutics

Over years, sleep medicine has been witnessing a great deal of advancement in therapeutics discovered against EDS disorder. Modafinil as a novel non-amphetamine wake-promoting drug replaced benzodiazepines which themselves have been initiated subsequent to the emergence of barbiturates (molecular genetic advances). Here, we discuss the molecular mechanisms of action of the wake promoting therapeutics used against EDS. The focus will be on modafinil, metamphetamine and orexin (68, 69).

- Modafinil

The precise mechanism of action of modafinil remains to be established. However several lines of evidence provide clues on how it may act. Modafinil has been reported to increase HA, NE, 5-HE, and DA levels in the brain, though some of these effects might be indirect. At least parts of the modafinil effect might be exerted through DAT and NET. Additionally, although orexin similar to modafinil has the wake-promoting effect, modafinil does not act through orexin and its receptors. Modafinil increases fos expression and HAergic tone in TMN, but this effect was not observed when the drug was administered directly into TMN. Modafinil also affects the glutamate level and this appears to be dependent on the brain region. However its effect on the GABA level is more consistent with no effect in the thalamus and hippocampus and a reduction in the cortex, medial preoptic area of the hypothalamus, posterior hypothalamus, nucleus accumbens, pallidum, and striatum. This effect presumably is mediated by serotonin (70).

Modafinil has neuroprotective (antioxidant) effects as well, but this might not be totally irrelevant to its wake-promoting effect. The target of antioxidant activity of modafinil is still not clear, but it may be the enzymes responsible for free-radical scavenging system. Since mitochondrion is the main source of the generation of free radicals, it is also possible that modafinil acts on the enzymes in this organ such as cytochrome c which affects the levels of free radicals and ATP. Similarly, modafinil may reduce the activity of the inhibitory K-ATP channels the suppress neurotransmitter release with the end result of increased neurotransmitter release. Furthermore modafinil may suppress other enzymes such as cytochrome p450 which has been shown to be a source of reactive oxygen species in coronary artery ischemia and reperfusion injury. CYP2C a member of C p450 family may also be involved in the metabolism of arachidonic acid in the brain and altering the effect of neurotransmitters. Therefore the inhibitory effect of modafinil might be exerted through this pathway. Modafinil may suppress CYP2C either directly or through the release of serotonin and epinephrine (40, 42, 71-75).

At least parts of the effects of free radicals might be exerted through an increase in extracellular level of adenosine; a sleep promoting factor throughout the brain. Although the antioxidant effect of modafinil might be scattered throughout the brain, since adenosine exert its sleep-inducing effect in the basal forebrain, this region might be mainly influenced by modafinil (40, 42, 71).

An alternative target of modafinil might be a receptor or an intracellular protein. One such candidate is sodium or calcium channels as changes in sodium homeostasis and calcium influx can affect neurotransmitter release. However this does not explain its neuroprotective effects. Accumulating evidence suggest that neurodegeneration and sleep may have a common or related mechanisms, thus there may be a single site of action for these phenomena. Sine mitochondria, oxidative stress and calcium homeostasis have also been implicated in the pathogenesis of a number of neurodegenerative diseases, it seems plausible that mitochondria is the main culprit both for neurodegeneration and sleep-inducing factors (76-83).

- Metamphetamines (MAs)

The vesicular monoamine transporter-2 (VMAT-2) and the plasmalemmal dopamine transporter (DAT) are the two main substrates of amphetamine on dopamine neuronal terminals. MAs are substrates of the Na+/Cl- dependent dopamine transporters. "Exchange diffusion model" predicts that metamphetamines compete with extracellular

synaptic dopamine on the DAT. Binding of extracellular MA to the DAT leads to the cytosolic dopamine to be reverse transported to the outside the cell. At higher concentrations, amphetamines can diffuse directly through the plasmalemmal membrane. According to this model, the DAT activity is regulated by cell signaling mechanisms such as calmodulin-dependent protein kinase-II and phosphotydyl inositol 3-kinase. Through another mechanism, DAT can assume a channel-like conformation, enabling brief release of dopamine as well. Furthermore MAs in-vitro can promote internalization of DAT through endocytosis which ablates the DAT capacity to decrease synaptic levels of dopamine(84). The VMAT-2, a membrane protein, transports monoamines from the cytosol into synaptic vesicles. This activity is coupled to a vacuolar type H+-pumping ATPase. Amphetamines at concentrations higher than 100 μM can disrupt the proton gradient between inside and outside of the vesicle leading to the monoamine leak into the cytosol. Additionally, multiple high doses of AMs (40mg/kg) lead to the redistribution of VMAT-2 to an unknown cellular location in a rat model. On the other hand, AMs at physiological concentrations bind to VMAT-2 and inhibit monoamine uptake in vesicles with the end result of increased cytosolic and synaptic monoamine concentration. MAs also influence DAT uptake through other proteins such as trace amine-associated receptor-1 (TAAR1). This is a G-protein coupled receptor for trace amines. Activated TAAR1 decreases DAT dopamine uptake, increases dopamine efflux, and promotes DAT endocytosis. MA is an agonist of TAAR1. Another mechanism of action of MAs is the inhibition of monoamine; an enzyme on the outer membrane of mitochondria with a role in amine catabolism in presynaptic terminals (85, 86).

- *Orexin*

Orexin has two G-protein coupled receptors, OX1R and OX2R. Distinct G protein may contribute to different physiological roles of orexin in certain neurons. Both voltage-dependent calcium channels and G-protein-gated inwardly-rectifier potassium channels (GIRKs) can be modulated by G-protein-coupled neurotransmitter receptors; however the receptors might be selectively coupled to one or more of the channels in neurons. Studies suggest that OX1R couples exclusively to PTX-insensitive G proteins, and OX2R couples to both PTX-sensitive and insensitive proteins. Several lines of evidence suggest that OX1R and OX2R signaling not only activate neurons but also may have other roles in the tips of developing neuritis and on presynaptic terminals. These functions eventually lead to growth cone collapse and increased release of neurotransmitters. Orexin in addition can cell-dependently increase or decrease cAMP which might be the result of coupling the receptor with different G-proteins. The latter might be influenced by the receptor density. Furthermore, orexin receptors can interact with other signaling receptors such as cannabinoid receptors which is reported to cause an enhancement of the orexin-A capability to activate the mitogen-activated protein kinase pathway. Therefore, such observations indicate that orexin signaling events might be more complex than initially thought (87-89).

Future directions in molecular research

Various eukaryotic model systems can be used to investigate the molecular mechanism of wake-promoting drugs. For example modafinil can promote wakefulness in fruit fly. The simplicity of this model compared with higher eukaryotes allows identification of the principle genes, proteins and pathways involved in wakefulness regulation (molecular genetics advances). Approaches such as

Large-scale random mutagenesis can be applied to identify some of the genes involved.

Yeast is the simplest eukaryote which can exist either haploid or diploid. This facilitates the study of the role of genes in cellular processes. Yeast can be grown with or without functional mitochondria and therefore may provide an ideal model to study the effect of modafil on mitochondria function and oxidative stress. Yeast can also be beneficial to study the mechanism of inhibition of monoamine oxidase by MAs as this enzyme can be expressed in yeast and its function can be studied in the presence of MAs.

Moreover, several proteins involved in waking/sleep states can be expressed in yeast. Some of which may then create a particular phenotype in yeast such as growth defect that can be overcome by complementation studies with a certain mammalian protein. This may provide the proteins associated with each other in the wake/sleep states and thereby provide evidence to understand the signaling pathways. The results obtained with the yeast model system can then be established in higher eukaryotes such as fruit-fly and zebrafish. Identifying the neurons responsible for drug's effect in fruit fly can pave the way to investigate the effect of other internal and external regulatory systems such as food, light, motivational states, homeostatic processes, circadian rhythms, and memory formation.

Table 1. An overview of the key features of the mostly-studied wake-promoting agents.

WPA molecule	Classes	Mechanism of action	Approval status	Advantages /Disadvantages	Reference
Modafinil (provigil®)	Non-sympathomimetic stimulants	Not clearly defined (Maybe blockade of dopamine transporters)	FDA approved for EDS in Narcolepsy, SWD and OSA (1988)	No evidence of tolerance and low potential for abuse / severe psychiatric side effects and skin reactions	39, 40-43
Armodafinil (NUVIGIL®)	Non-sympathomimetic stimulants	As same as modafinil	FDA approved for EDS in Narcolepsy, SWD and OSA (2007)	Longer half-life than modafinil	52
Amphetamin (Benzedrine® Adderall®)	Indirect-acting sympathomimetics	At low doses, release dopamine and to a lesser degree, norepinephrine. At higher doses, monoaminergic depletion and inhibition of reuptake	Since 1937 used for narcolepsy, FDA approved for ADHD (2002)	Potency /high potential for recreational abuse	55
Methylphenidate N-methyl derivative of amphetamine (Ritalin®)	Indirect-acting sympathomimetics	Blocking of the reuptake of monoamines (mainly dopamine) and, unlike amphetamines, does not inhibit the vesicular monoamine transporter	Used since 1970 (1982)	Shorter half-life, milder side effects, and low abuse potential than amphetamine/	58-59
Caffeine/Paraxanthine	Indirect-acting sympathomimetics	Adenosine A1 and A2a receptor antagonist	The earliest used stimulants	Low potency and cardiovascular side effects	65
Gamma hydroxybutyrate	Direct-acting sympathomimetics	$GABA_B$ receptor agonist	Approved for narcolepsy by EMA and for cataplexy by FDA (1990)	Readily crosses the blood-brain barrier /Controversial concern about great potential in date rape and misuse in athletes for its metabolic effects	59
Pitolisant	Not classified	Histamine H3 inverse agonist	Passed phase III clinical trials for the treatment of EDS and narcolepsy	Hope for new treatment option	66, 67

Zebrafish is particularly-useful model for studying the effect of small molecule on wake/sleep states. This approach in combination with the gene expression profiling can identify the drug-activated neurons. Subsequently, gene ablation methods can determine whether the gene is essential for drug-induced effect.

Additionally, viral-mediated focal replacement of certain genes in this model can provide valuable information for deciphering the wake/sleep circuitry. Since there is significant homology between zebrafish and mammalian brain structure, observations made in this model can have correspondence in mammals.

Conditional knockout technology in which viruses injected in the brain of adult mice provides both temporal and spatial control of wake/sleep gene function. Moreover siRNA-mediated mRNA knockdown has facilitated investigating the function of certain proteins and receptors.

Another approach is comparing the transcriptome/proteom profile of the wakefulness with the sleep state. This has already resulted in the identification of several genes associated with either wakefulness or sleep state. Genes such as those responsible for expressing cytokines, TNFR1, TNFR2, TNF-α, and lymophotaxin which regulate the wake/sleep state can also be studied using mutagenesis as well as polymorphism and association with known wake/sleep genes.

Optogenetic inhibition or activation of the desired genes permits identification of drug targets without altering the function of a certain gene for good. However studying wake/sleep states through "locus by locus" approach might be hindered by the redundancy of the circuitry involved (87-89).

Conclusion

The present review was an attempt to provide an overview on wake-promoting therapeutics within the basic-clinical spectrum. The use of wake-promoting agents in the event of EDS need to be carefully assessed since it may masquerade the underlying sleep-related disorder. Novel therapeutics in this vein are being developed through targeting new molecular targets. Given the health-related and societal consequences of EDS, basic, translational and clinical research to unravel its various dimensions should gain impetus.

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