The Perfect Hypnotic?
Emmanuel Mignot
Science 340, 36 (2013);
DOI: 10.1126/science.1237998

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by clicking here.

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines here.

The following resources related to this article are available online at www.sciencemag.org (this information is current as of April 4, 2013):

Updated information and services, including high-resolution figures, can be found in the online version of this article at: http://www.sciencemag.org/content/340/6128/36.full.html

This article cites 14 articles, 4 of which can be accessed free: http://www.sciencemag.org/content/340/6128/36.full.html#ref-list-1

This article appears in the following subject collections:
Physiology
http://www.sciencemag.org/cgi/collection/physiology
The Perfect Hypnotic?

Emmanuel Mignot

The market for hypnotics is big business, with 10 to 15% of the population in the United States suffering from chronic insomnia (1, 2). Although the pathology is unknown, and likely heterogeneous, patients with insomnia are in a state of hyperarousal (even during the day), suggesting that wake-promoting systems are hyperactive (3). The search for the ideal hypnotic has been marked by cycles of elusiveness followed by disappointment, as adverse side effects associated with each new class of drug have emerged following wide use. Although insomnia therapy increasingly uses cognitive behavioral therapy, the enormous number of sufferers mandates new pharmacological approaches. Uslaner et al. (4) report the prospect of a new class of compound with a new mode of action that may usher in a new era for insomnia treatment, with the potential for fewer side effects.

At the beginning of the 19th century, chloral hydrate, meprobamate, and barbiturates were touted as nonaddictive miracle tranquilizers, but in the 1950s, their potential for tolerance and severe addiction was recognized (5). At high dose, they lead to pulmonary arrest and death, outcomes that gained further notoriety with the deaths of celebrities Marilyn Monroe and Jimi Hendrix. Broad inhibition of brain activity through high-dose barbiturates can even induce a “flat” electroencephalogram mimicking brain death. Barbiturates activate a chloride channel receptor for gamma-aminobutyric acid [type A (GABA_A)]. GABA is the main inhibitory neurotransmitter, produced by 15 to 20% of all brain neurons.

Hope for a safe, effective hypnotic reemerged with chlordiazepoxide, the first benzodiazepine [(BDZ); a two-benzene ring structure linked by a third, diazepine ring].

References
BDZs are safer, rarely causing respiratory depression, even when “overdosed,” and more than 40 derivatives (including the prototypic diazepam) have been synthesized. Prescribed variously for sleep induction or maintenance, as anticonvulsants, muscle relaxants, or as anxiolytics, these drugs were proclaimed as the perfect solution. But they too fell out of favor when long-acting compounds were found to induce residual sedation, memory loss, and addiction. BDZs bind to the GABA_2 receptor at a site that is different from that for barbiturates, yielding similar but less extensive effects (5, 6). The residual effects, however, spurred development of short-half-life hypnotics in the 1980s (e.g., triazolam). Although effective, these compounds manifested other problems: rebound insomnia on cessation and occasionally a state of “confusional arousal” in which the patient may be acting out unaware, half-asleep but moving around, not unlike sleep-walking (this led to legal cases). Triazolam was withdrawn from many markets and/or the dose decreased.

Then came the “Z-drugs”—zaleplon, zolpidem, and zopiclone (and eszopiclone)—short-half-life compounds with lower effective doses and improved side-effect profiles. Although lacking the three-ring BDZ structure, they recognize the BDZ-binding site of the GABA_2 receptor and manifest receptor subtype specificity such that some have primarily hypnotic (zolpidem) rather than both hypnotic and anxiolytic (eszopiclone) effects (6). Although safer than classic BDZs, occasional problems with dependence, tolerance, and “confusional arousals” are still reported with Z-drugs in at-risk populations. These BDZ-like compounds are now the “gold standard” treatment for insomnia, although they are “scheduled” substances by the U.S. Food and Drug Administration (their use and distribution are tightly controlled because of abuse potential) and viewed with some suspicion by doctors and patients.

In parallel with this drug evolution, sedatives (e.g., chlorpromazine) were introduced to treat agitation in psychotic patients in the 1950s. These compounds block receptors for the neurotransmitter dopamine, although sedative effects mostly correlate with their ability to block H1 histaminergic receptors that relay wake-promoting histamine signals within the brain. Antihistamines were developed to treat allergies but soon found utility as remedies for insomnia. More “natural” sedatives, such as the hormone melatonin, have a modest hypnotic effect, typically insufficient for severe insomnia, although typical doses far exceed normal physiological amounts. Melatonin or melatonin agonists (such as ramelteon) activate cognate receptors in the brain to provide a “darkness” signal that may be useful, when combined with light therapy, to adjust circadian rhythms. Similarly, wary of addiction to GABAergic drugs, many patients are prescribed sedative antidepressants that block the H1 histamine or the 5-hydroxytryptamine (5HT2) serotonin receptors. These compounds were never developed for insomnia, and have long half-lives, thus causing residual daytime sedation (5).

Uslaner et al. (4) explored the effects of a new class of hypnotic compounds that are antagonists of the two receptors for orexin, so-called dual orexin receptor antagonists (DORAs). Orexins (also called hypocretins) are key neurotransmitters of arousal in the central nervous system. Genetic and pharmacological studies pointed to modulation of the orexin system as potential therapy for insomnia and other sleep disorders (7, 8). DORAs have fewer effects on daytime performance tests, and no rebound insomnia on cessation (9), although there are residual dose-dependent sedative effects (10), and high doses administered during the day can impair human performance. Uslaner et al. (4) compared the effects of DORA-22 with those impaired by diazepam, zolpidem, and eszopiclone but not by DORA-22. Similarly, the ability of monkeys to remember and match colors after a small delay (a working memory task) or to react rapidly to the appearance of an object on a screen (a measure of attention) was not impaired by DORA-22, whereas all GABAergic treatments had substantial detrimental effects. What is needed next are parallel studies in humans to demonstrate generalization to a clinical population.

Unlike the broad inhibitory effects of GABA on brain activity, orexins produce selective wake-promoting signals. Although orexins are produced by only 70,000 neurons in the hypothalamus, these send widespread anatomical projections, thereby exciting other wake-promoting systems such as the histaminergic tuberomammillary nucleus, the adrenergic locus coeruleus, and various cholinergic and aminegic cell groups. Blocking orexin may thus be closer to treating the underlying issue of excess alertness in insomnia compared to promoting sleep by inhibiting brain activity.
Discovered in 1998 (11, 12), the role of orexins (there are two types, A and B, processed from the same pre-propeptide) in sleep emerged when it was discovered that impaired orexin signaling results in the sleep disorder narcolepsy in animal models and humans (7). Narcolepsy is characterized by sleepiness and abnormal rapid eye movement (REM) sleep, so that patients not only fall asleep easily but also experience symptoms where REM sleep intermingles with wakefulness, resulting in dream-like hallucinations or episodes of muscle paralysis when awake (sleep paralysis and cataplexy). Narcolepsy is caused by an autoimmune attack against neurons that express orexin.

Orexins act on G protein–coupled receptors called hypocretin receptor 1 and 2 (also called OX1R and OX2R, respectively). Although OX2R is more prominently involved in narcolepsy, both receptors may regulate sleep, although this could be species dependent. The potential for orexin antagonists to increase REM sleep and dreaming, or even narcolepsy-like symptoms, has been a concern (8), but has not been observed to a substantial degree in clinical trials with DORA molecules (13). A small but significant increase in REM sleep and decreased REM latency were noted, and sleep may be less consolidated than after GABAergic hypnhetics (9, 10, 13). As the beneficial effects of REM versus non-REM sleep on restoration of wakefulness, memory, synaptic plasticity, and mood are highly debated (14, 15), it is uncertain whether this difference in REM versus non-REM profile may be beneficial.

Are DORAs the perfect hypnotics? Only long-term use in large numbers of insomnia patients will reveal whether these drugs will be preferred to GABAergic hypnhetics, and whether they produce rare complications, including narcolepsy-like symptoms in predisposed individuals (16). Side effects are expected with any active treatment, and the benefit-risk ratio must be considered. There is minimal tolerance for side effects and risk in the treatment of insomnia, so distinct drugs offering multiple modes of action, especially complementary ones, will greatly benefit patients.

References and Notes
16. The U.S. Food and Drug Administration is currently reviewing an application for the use of a DORA in insomnia, based on the result of a phase III clinical trial; www.businesswire.com/news/home/20121108005310/en/Merk-Announces-FDA-Acceptance-Drug-Application-Suvorexant. 10.1126/science.1237998

MICROBIOLOGY

Breathing Perchlorate

Robert Nerenberg

About 20 years ago, investigators discovered that perchlorate (ClO₄⁻), a synthetically produced chemical widely used in rocket propellants and explosives, was present at trace levels in many water supplies across the United States (1). Perchlorate can inhibit thyroid function, potentially leading to developmental problems in fetuses and infants (2). The public outcry led to intense research on perchlorate and the environment. Biological reduction was considered a promising treatment strategy for perchlorate, as well as for a related oxianion, chlorate (ClO₃⁻) (1, 3). This approach is based on microorganisms that can respire on, or gain energy from, the reduction of these compounds to chloride. On page 85 of this issue, Liebensteiner et al. show that the hyperthermophilic archaeon Archaeoglobus fulgidus can also respire with perchlorate and chlorate (4). This discovery changes several paradigms about perchlorate and chlorate-reducing microorganisms.

An archaeon with an unusual perchlorate-reducing metabolism raises questions about the diversity and evolution of perchlorate-reducing microorganisms.

Early studies on the microbial reduction of perchlorate and chloride showed that denitrifying bacteria could reduce perchlorate and chlorate with the nonspecific nitrate reductase enzyme (5). However, the end product was chloride, a reactive and toxic intermediate. This explained why denitrifying bacteria reduced perchlorate for a limited time and without growth. Other bacteria were found to have a dedicated pathway for perchlorate and chlorate reduction that allowed continued and vigorous growth (6). In this case, the end product was nontoxic chloride. (Per)chlorate-reducing bacteria (the collective name for bacteria that reduce perchlorate and chlorate) prefer to respire on oxygen, if present; most can also grow via reduction of nitrate (NO₃⁻), or denitrification. Their abundance in pristine soil and water environments was explained when it

Diversity of (per)chlorate reducers. Phylogenetic tree showing the positions of known (per)chlorate-reducing microorganisms. Liebensteiner et al.’s discovery of a (per)chlorate-reducing archaeon expands the diversity of these microorganisms to a second domain of life.

Department of Civil and Environmental Engineering and Earth Sciences, University of Notre Dame, Notre Dame, IN 46556, USA. E-mail: nerenberg.1@nd.edu

An archaeon with an unusual perchlorate-reducing metabolism raises questions about the diversity and evolution of perchlorate-reducing microorganisms.