

Adrafinil: A Novel Vigilance Promoting Agent

Norton W. Milgram, Heather Callahan, and Christina Siwak

*Division of Life Sciences, University of Toronto at Scarborough,
Toronto, Ontario, Canada*

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INTRODUCTION

Behavioral stimulants have widespread potential application in the treatment of affective disorders, disorders of vigilance, and disorders of sleep. Most behavioral stimulants, however, must be used with extreme caution because of undesirable side effects that include stereotypy, anxiolytic effects, and addiction. Adrafinil, developed in France by Louis Lafon Laboratories, is a novel pharmaceutical that has behavioral-activating effects but lacks the undesirable side effects of other stimulants. Peripheral sympathomimetic effects are also absent in subjects treated with adrafinil. Jouvet (36) introduced the term “eugrégorique” (eugregoric in English) to characterize this unique type of arousal-producing agent, but the term is not widely used in the scientific literature.¹ There have not been many published studies on adrafinil, and the large majority of studies have been published in French. Human studies indicate that adrafinil has clinical efficacy as a vigilance-promoting and mood-enhancing agent in the elderly. As an area for therapeutic intervention, vigilance enhancement has received much more attention in Europe than in North America. Somewhat surprisingly, perhaps, adrafinil is known to a larger nonscientific audience, where it is considered to be a nootropic agent.

The literature on modafinil, the primary metabolite of adrafinil is much more extensive. This work has largely focused on the potential application of modafinil in the treatment of sleep disorders, and modafinil has recently received regulatory approval for the treatment of narcolepsy in the United States. Since the types of clinical trials that have been conducted differ (vigilance enhancement for adrafinil vs. narcolepsy for modafinil), it is not clear whether modafinil effectively replaces adrafinil or whether the two compounds are uniquely valuable for different applications. Most investigators assume that

Address correspondence and reprint requests to Prof. N. W. Milgram, Division of Life Sciences, University of Toronto at Scarborough, 1265 Military Trail, Scarborough, Ontario M1C 1A4, Canada.
Fax: (416) 287-7642. E-mail: milgram@psych.utoronto.ca.

¹ The origins come from the Greek “eu” meaning good and “gregor” meaning wakening.

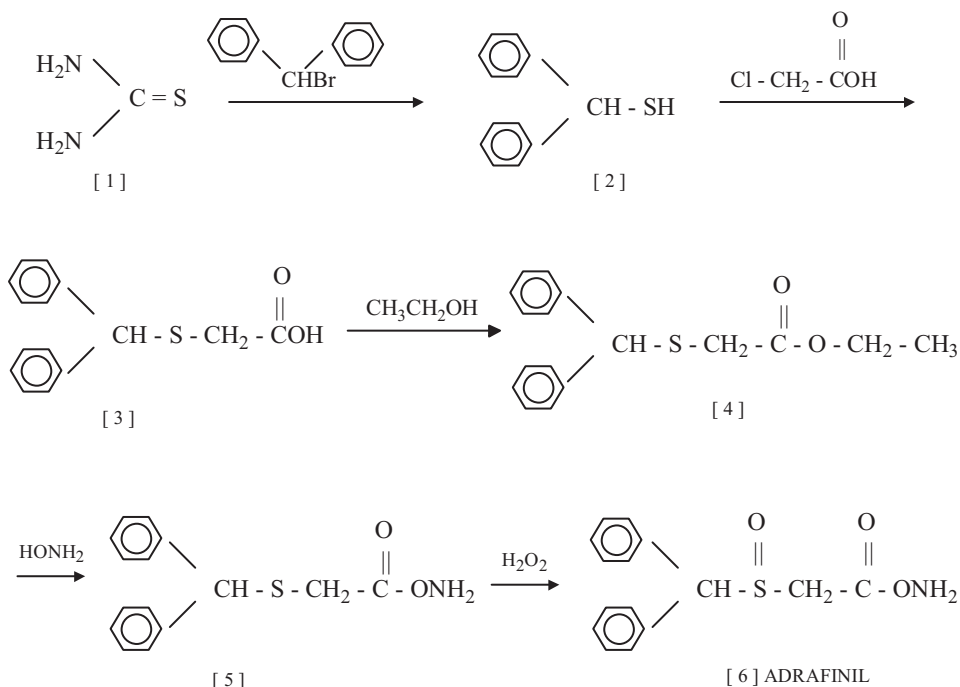


Fig. 1. Chemical structure and synthesis of adrafinil. A six step process is used in synthesizing adrafinil. [1]Thiourea is reacted with bromodiphenylmethane over heat to produce [2] diphenylmethane-thiol. Chloroacetic acid is then added to the product to form [3] benzhydryl-thioacetic acid, which is alkylated to [4]ethyl benzhydryl-thioacetate. This compound reacts with hydroxylamine to form [5] benzhydryl-thioacetohydroxamic acid. A final oxidation converts the product to [6] benzhydrylsulfinyl-acetohydroxamic acid.

adrafinil and modafinil both serve as α_1 -adrenergic-receptor agonists. The evidence in support of this hypothesis, however, is weak, and other mechanisms of action are probable. This review focuses primarily on adrafinil, but it also reviews studies on modafinil that help to clarify the underlying mechanisms of action of adrafinil. This review also considers potential novel applications of adrafinil in the treatment of disorders associated with dementia.

CHEMICAL STRUCTURE

Adrafinil (CRL 40028) is a white-to-rosy-beige crystalline powder, with a light sulfurous odor; it was synthesized by Louis Lafon Laboratories. The proprietary name of adrafinil is Olmifon[®]; its chemical name is (*diphenylmethyl*)sulfinyl-2-acetohydroxamic acid (see Fig. 1). This compound has a molecular weight of 289.35, and its empirical formula is C₁₅H₁₅NSO₃. It has a melting point of 154°C with decomposition and is slightly soluble in water (< 1 g/L), more soluble in ethanol, and soluble in methanol.

The synthesis of adrafinil is summarized in Fig. 1. Thiourea (1) is reacted with *bromodiphenylmethane* over heat to produce *diphenylmethane-thiol* (2). *Chloroacetic acid*

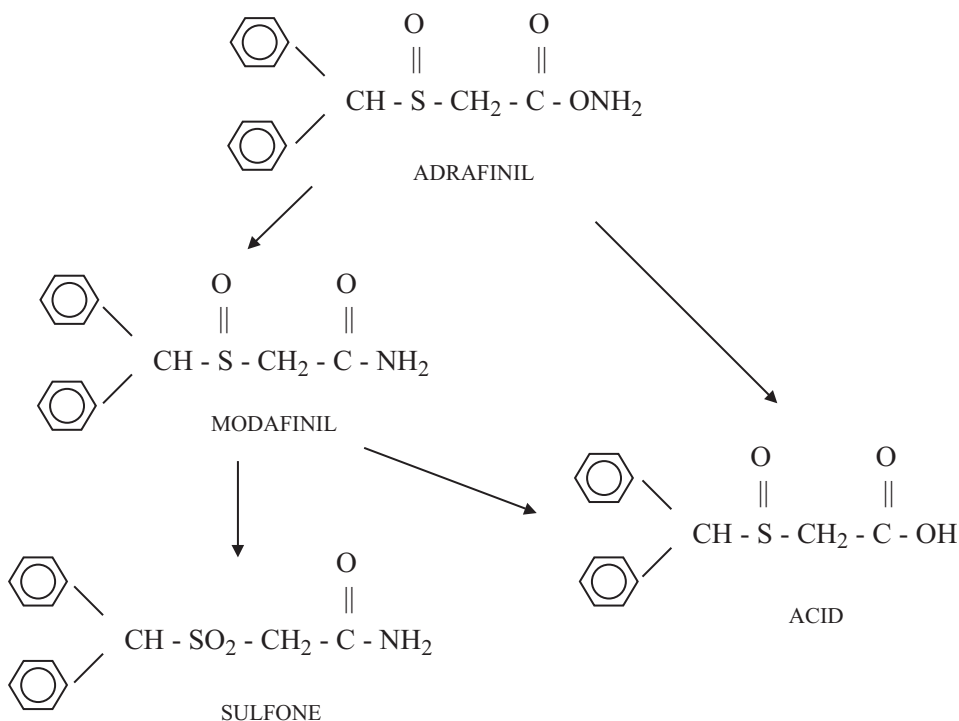


Fig. 2. Metabolism of adrafinil. This figure illustrates the two possible metabolic pathways for adrafinil that lead to either an acid or a sulfone.

is then added to this product to form *diphenylmethyl-thioacetic acid* (3), which is alkylated to ethyl *diphenylmethyl-thioacetate* (4). This compound reacts with *hydroxylamine* to form *diphenylmethyl-thioacetohydroxamic acid* (5). A final oxidation step converts this product to *(diphenylmethyl)sulfinyl-acetohydroxamic acid* or adrafinil. The final compound is crystallized, recovered by filtration, and then purified by recrystallization in ethyl acetate and isopropyl ethanol. As illustrated in Fig. 2, orally administered, adrafinil (CRL 40028) is metabolized into an amide (CRL 40476) and an acid (CRL 40467) form. The acid form is *(diphenylmethyl)sulfinyl-2-acetic acid* (47). The main metabolite is the amide form (CRL 40476), called modafinil [*(diphenylmethyl)sulfinyl-2 acetamide*]. Modafinil is also metabolized into acid and sulfone forms, which are both inactive (10).

TOXICOLOGY AND PHARMACOKINETICS

No toxic signs were seen in subacute toxicological studies with doses of 100, 200, and 400 mg/kg in rats treated over 1 month or with doses of 50, 100 and 200 mg/kg adrafinil administered over 3 months. Some instances of hyperactivity and stereotypical behavior were observed in studies with dogs given doses of 50, 100, and 200 mg/kg administered over 2 months or doses of 20, 50, and 75 mg/kg of adrafinil administered over 3 months.

Some fatalities were seen at a dose of 200 mg/kg of adrafinil. No mutagenic effects, peri- or postnatal effects, or teratological effects were observed (49).

LD₅₀ levels vary widely among species. In mice and rats, the LD₅₀ is approximately or slightly greater than 1250 mg/kg (49). The oral LD₅₀ for rats is 3400 mg/kg. As one indication of the safety level of modafinil in humans, Bastuji and Jouvet (2) described a subject who unsuccessfully attempted to commit suicide by taking 45 tablets of modafinil (a quantity 15 times greater than a normal high dose). Bastuji and Jouvet (2) also found that the long-term use (≥ 3 years) of modafinil did not result in harmful side effects, peripheral side effects or disturb nocturnal sleep. Patients treated with modafinil for at least 3 years did not develop tolerance or dependence.

Moachon et al. (44) found that adrafinil and modafinil have elimination half-lives of 1 and 3 h, respectively. There is no evidence of sex differences in regard to the pharmacokinetics of these agents. Saletu et al. (49) found that plasma levels peaked at about 1 h after oral administration of 900 mg/kg of adrafinil. The plasma levels of the two metabolites of adrafinil, modafinil, and CRL 40467, peaked later. The peak plasma concentration of adrafinil preceded peak behavioral and EEG response by about 1 h. This finding raises the possibility that the conversion of adrafinil to modafinil, the primary metabolite, is responsible for much, if not all, of the behavioral effects of adrafinil. This suggestion is supported in the few studies that have shown that the response to adrafinil directly compares to the response to modafinil (12). However, Ferner et al. (24) have found the serum levels of adrafinil to be a better predictor of its effect on EEG response than the serum levels of modafinil; the subjects with the lowest serum concentrations of adrafinil showed the least pronounced effects.

Siwak et al. (54) have looked at plasma concentrations of adrafinil, modafinil, and CRL 40467, at 2 and 10 h after treatment with adrafinil at doses of 10, 20, 30, and 40 mg/kg in the dog. Blood samples were taken 2 h following dosing on days 1 and 9 of treatment and 10 h following dosing on days 4 and 13.

Consistent with previous findings, plasma concentration of adrafinil decreased more rapidly than the plasma concentration of either metabolite. The time-dependent changes in plasma levels also varied as a function of dose but in a complex way. At 2 h, there was a direct relationship; the higher dose correlated with the higher concentration. This was not the case at 10 h, where a U-shaped relationship was observed; a lower concentration of adrafinil was seen following treatment with 40 mg/kg than after treatment with 10 mg/kg. Compared to the high and low dose, doses of 20 and 30 mg/kg produced higher plasma levels of adrafinil. Siwak et al. (54) also found changes in the rate of metabolism after repeated administration. Serum levels of adrafinil were higher and showed a lower rate of decline after repeated treatment than after initial treatment. Finally, there were often marked individual differences in serum levels, which correlated with individual differences in behavioral responsiveness. There are several possible explanations for these unusual effects. For example, adrafinil may act as an enzyme inducer at high concentrations only. Future studies should examine this possibility.

The amount of pharmacokinetic data on adrafinil is limited and more research is necessary. Since adrafinil is a CNS-active drug, it may be particularly useful to know more about its time course and brain distribution following its administration.

PHARMACOLOGY

Behavioral Activity

In animal studies the most striking behavioral response to adrafinil is increased activity. This was first noted by Duteil et al. (21), who reported a dose-dependent increase in activity at doses of 64 and 128 mg/kg in mice. Using the number of photocell beam interruptions as a measure of activity, Rambert et al. (48) found that activity increased at doses between 64 and 256 mg/kg. Milhaud and Klein (41) looked at the effect of adrafinil on nocturnal activity in the monkey, and they found that a 60 mg/kg dose approximately doubled activity, while doses of 90 and 120 mg/kg increased activity by a factor of four. The effect of the 60 mg/kg dose was significantly different from baseline only after the second treatment. The higher doses produced significant effects after the first treatment. Similar effects have also been found in rats (17).

These behavioral activating effects of adrafinil differ from those of other psychostimulants in two essential ways. First, unlike amphetamine, adrafinil does not generally produce stereotypical behavior (47), except possibly at very high doses. Second, the effects of adrafinil are not anxiogenic. This was shown by Hascoët and Bourin (33), who found that adrafinil did not affect the proportion of total activity spent in the dark compartment of a test chamber compared to activity spent in the light compartment. Amphetamine, in contrast, caused a proportionately greater increase in activity in the dark compartment, which is indicative of an anxiolytic effect.

Siwak et al. (53) have looked at the effect of adrafinil on behavioral activity in the dog in two separate studies. In the first study, adrafinil was orally administered to older dogs for 14 consecutive days. Increased locomotor activity was seen at dose levels between 20 and 40 mg/kg. This effect was generally unaccompanied by stereotypical behavior in the test session. There was some variability; a subpopulation of animals showed either no effect or decreased locomotion after treatment with adrafinil.

In this study, locomotion, as well as other behaviors, were measured by direct observation. The results suggested that the activity-enhancing effect of adrafinil was specific to locomotion; adrafinil did not cause a consistent increase in any other behavior. Thus, sniffing showed only a transient increase, and vocalization, grooming, jumping, and rearing showed no consistent effect. Siwak et al. (53) also found a decrease in frequency of urination, but this occurred only at the highest dose.

A second study compared the effects of adrafinil with two other drugs that purportedly serve as activity-enhancing agents — nicergoline and propentofylline (54). The treatments were administered daily over 33 days, and both open field and home cage activity were observed. The results of the open field activity are shown in Fig. 3; adrafinil produced a marked and sustained increase for the duration of the study. Neither of the other two drugs produced any effect.

The effect of adrafinil in the home cage test, by contrast, was much smaller. A statistically significant increase was achieved only when the activity analysis combined data from both morning and afternoon home cage tests.

Not all investigators have found that adrafinil increases locomotion. Edgar and Seidel (22) found generally parallel effects on sleep and locomotion in rats following treatment

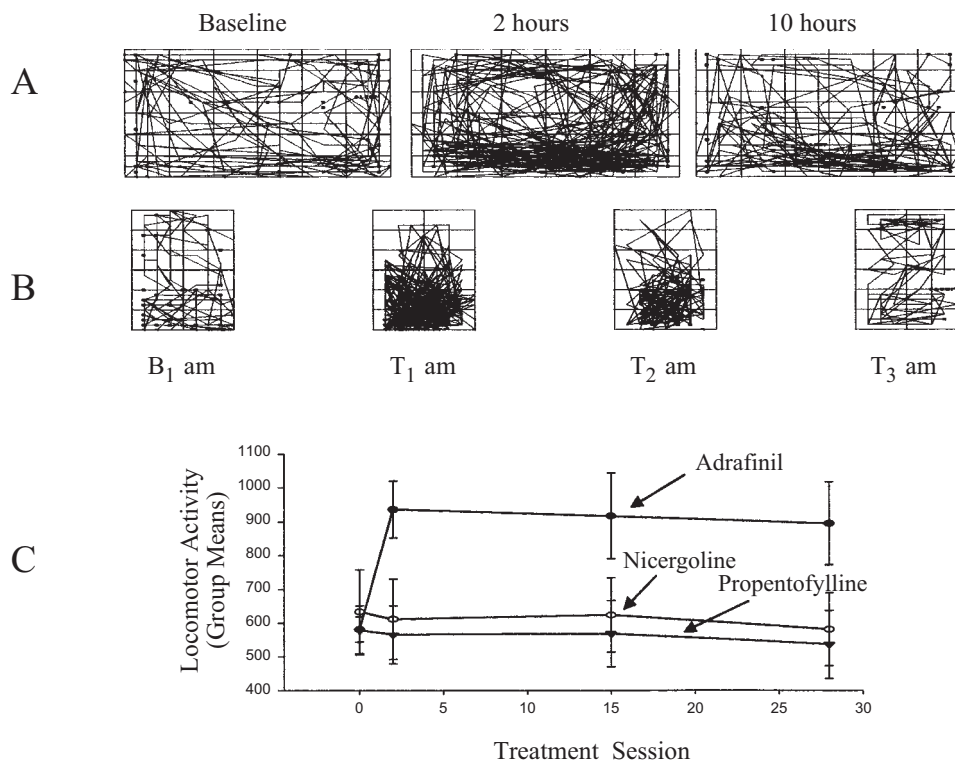


Fig. 3. Effects of adrafinil on locomotion in beagle dogs, and a comparison with other activity promoting agents. (A) shows activity pattern in the open field under placebo control, 2 h, and 10 h following treatment with adrafinil. The activity pattern is a computer-assisted tracing of total movement during a 10-min test session. (B) shows home cage activity patterns for one animal under placebo control and on three separate tests with adrafinil. Note the variability in response, which is typical in the home cage but not open field. (C) compares the effects of adrafinil, propentofylline, and nicergoline on locomotor activity in the open field test over repeated testing. Although all three are putative activity enhancing agents, only adrafinil produced consistent significant effects.

with modafinil; an increase in locomotion was accompanied by a decrease in sleep. These observations raised the possibility that locomotion increased simply because the animals were awake for a longer period of time. In fact, modafinil had no effect on activity when they looked only at rate of activity during the awake time.

Environmental context probably contributed to the data of Edgar and Seidel. Their behavioral measurements were all taken when the animals were undisturbed in their home cages. Most reports of increased activity, by contrast, have been based on measurement in an activity recording chamber, which is a novel environment. The importance of test location was also seen in the work of Siwak et al. (53,54), which showed a greater effect of adrafinil on canines in open field locomotion than on home cage activity. The difference between the two conditions is environmental context, which is familiar in the home cage test but novel in the open field. According to this hypothesis, increased locomotion in the open field is a reflection of increased exploratory behavior. Such an increase is not seen in the home cage test because the observations are made in a highly familiar environment.

The environmental context hypothesis can also account, at least in part, for individual differences in open field behavior. An occasional canine subject shows a fearful response to the open field; such dogs are less likely to show an increase in locomotor activity when treated with adrafinil. Presumably, the environmental context is different for these dogs, than for dogs that do not show a fearful response to the open field.

Some of the diversity in the activity data may also reflect differences between modafinil and adrafinil. Increased activity has been reported in every published study of adrafinil. Edgar and Seidel (22) tested modafinil. In another negative report, using a range of doses, Shelton et al. (50) found that modafinil had no effect on open field activity in dogs. However, this finding could have been an anomalous consequence of using dogs that were narcoleptic; they also found that modafinil did not affect catalepsy in these dogs.

Other Behavioral Effects

Most activity studies involve automated activity measuring devices, which are unable to distinguish locomotor activity from other behavioral activity. While, locomotor activity, in most instances, is likely to account for increased activity; other behaviors are also affected by adrafinil. These behaviors are affected less consistently, generally at higher doses, and the effect is often inhibitory.

Rambert et al. (47) found that adrafinil had no effect on stereotypical behavior or climbing activity. Delini-Stula and Hunn (17) reported that adrafinil suppressed apomorphine-induced yawning, which was replaced by stereotyped gnawing, licking and sniffing. As previously mentioned, Siwak et al. found that adrafinil has little effect on grooming, sniffing, jumping, and vocalization in dog. Siwak et al. did, however, find that adrafinil has an effect on urination frequency, which decreased but only at the highest dose level.

There is some indication that adrafinil affects basic motivational states. According to Saletu et al. (49), two subjects reported that they experienced interest in sex for the first time in years after taking adrafinil. Nicolaidis and de Saint Hillaire (45) found decreased feeding and body weight following treatment with modafinil. Surprisingly, the dose-response curve was U-shaped, with decreases seen at 20 and 40 mg/kg but not at doses of 10 and 80 mg/kg.

Learning and Memory

We have not found any published studies on animal models that have addressed the effects of adrafinil on learning or memory. There is, however, evidence that behavioral stimulants such as amphetamine facilitate learning (20,55).

To examine the effect of adrafinil on learning, we trained aged beagle dogs on size and intensity discrimination learning tasks, with the training sessions given 2 h following treatment with either 20 mg/kg of adrafinil or a placebo control. A crossover design was used so that every animal was tested under both adrafinil and placebo control conditions. Treatment with adrafinil produced significant improvement in learning as indicated by a

decrease in both errors and trials to criterion. This improvement also appeared to be related to baseline cognitive function: the most severely impaired dogs appeared to show the greatest improvement. An effect of adrafinil on motivation, vigilance or both may account for these findings (42).

Sleep Suppression and EEG

As previously stated, adrafinil increases night-time activity, which is indicative of reduced sleep. Most subsequent research on sleep suppression has focussed on modafinil and its possible applications in treating sleep disorders. In narcoleptics, modafinil has been found to be effective in reducing excessive daytime sleepiness (2,6), without affecting the quantity or quality of nocturnal sleep (9) and without affecting blood pressure or heart rate.

EEG and Sleep

A study by Ferner et al. (24) was the first to examine the electrophysiological effects of adrafinil. They found progressive decreases in slow wave activity (0.5–7.5 Hz) for the first 2 h following treatment with either 600 or 1200 mg doses of adrafinil. A more detailed spectral analysis of its EEG effects was reported by Saletu et al. (49). They confirmed that adrafinil caused a decrease in slow waves in the delta and theta frequency bands, and they also found a decrease in the very fast beta activity. By contrast, alpha activity increased and there was a trend towards an increase in slow beta activity.

Callahan et al. (11) have recently looked at the effect of adrafinil on resting EEG in aged dogs. Three aged dogs were given 10 mg/kg of adrafinil and their resting EEG was measured for 0–5 h after treatment. A computer-assisted power spectrum analysis indicated that adrafinil caused an increase in alpha and beta activity and a decrease in delta and theta activity, which were the same results obtained by Saletu et al. (49) with humans. Callahan et al. also found, however, differences between dogs that were correlated with the frequency composition of the baseline EEG. Dogs with an initial EEG composition consisting of a predominantly low frequency showed a greater increase in alpha and beta activity than dogs that had a high alpha and beta activity prior to drug treatment.

Findings of Callahan et al. are consistent with research that has examined the effects of modafinil on narcoleptic dogs. In canine narcolepsy, modafinil increases wakefulness and reduces slow-wave sleep but is unable to suppress cataplexy (50). This finding has also been seen in humans with narcolepsy (2,5,6).

MECHANISMS OF ACTION

Adrafinil is widely believed to serve as a selective α_1 -adrenergic receptor agonist. Recent work, however, has suggested at least two other possible mechanisms of action:

adrafinil may modify the intracerebral release of amino acids (both GABA and glutamate) and adrafinil may increase cerebral metabolism. In this section, these three hypotheses and the evidence that localizes the site of action of modafinil to restricted CNS regions will be reviewed.

The α_1 -Adrenergic Receptor Hypothesis

Duteil et al. (21) reported that phenoxybenzamine, prazosin, and yohimbine, all α -adrenergic antagonists, were able to block the activity-enhancing effect of adrafinil. A more selective effect on α_1 receptors was suggested by Chermat et al. (13). They found that adrafinil blocked convulsions in quaking mice (neurological mutants of the C57 BL/6J strain) and that this effect was antagonized by prazosin, a selective α_1 -receptor antagonist. The utility of the quaking mouse as a model for studying adrenergic receptors has been previously demonstrated (19,51).

Other evidence consistent with the α_1 -adrenergic receptor hypothesis includes similarities in behavioral responses produced by adrafinil and behavioral responses resulting from α_1 agonists. These responses consist of decreased immobility during a forced swimming test and increased locomotion (47). Furthermore, the behavioral effects of adrafinil are inhibited by selected α_1 -adrenergic receptor antagonists, in particular, prazosin. These include the locomotor-enhancing effects (48).

The α_1 -adrenergic-receptor hypothesis has difficulty accounting for a number of findings. The first is an absence of peripheral adrenergic effects. This has been a highly consistent finding. Duteil et al. (21) found no indication of salivary viscous secretion, contraction of pilomotor muscle, or exophthalmos. Similar findings were reported in other studies (47). The suggestion that adrafinil does not have peripheral adrenergic effects is also supported by evidence that α_1 -adrenergic receptor agonists do not block all of the effects of adrafinil. Chariot et al. (12) found that adrafinil inhibited pancreatic secretions, and this was not prevented by treatment with prazosin. In fact, this effect of adrafinil on secretion is opposite to what is normally expected of an α -adrenergic agonist.

A second problem was indicated in a study by Akaoka et al. (1), who failed to detect any effects of modafinil on firing rate of noradrenergic neurons in the locus coeruleus and dopaminergic neurons in the midbrain. By contrast, amphetamine caused a potent inhibition of neuron firing, which confirms that these neurons were catecholaminergic. This result is consistent with receptor binding studies which, although limited in number, also do not support an α_1 agonistic mechanism of action (40).

Finally, the effects of adrafinil can be blocked by drugs that do not affect adrenergic transmission. Hascoët et al. (34) found that locomotor activity in mice was blocked by σ agonists, which suggests that adrafinil has an effect on opioid receptors.

Effects on Amino Acid Neurotransmitters

The research summarized here deals only with modafinil because parallel studies have not been done with adrafinil. These studies indicate that modafinil affects release of both

excitatory and inhibitory amino acid neurotransmitters and these effects can vary between brain structures.

A γ -aminobutyric acid (GABA) hypothesis of action was first proposed by Tanganelli et al. (54). They found that modafinil inhibits the cortical release of GABA and this effect was not blocked by prazosin. This increased inhibition is opposite to what is expected from an α_1 -adrenergic agonist (3). Subsequently, reduced GABA release was also reported in hypothalamic structures (25), the neocortex (57), nucleus accumbens (26), and striatum (28).

Further support for a GABA hypothesis was provided by Ferraro et al. (26). They found that modafinil enhanced basal release of dopamine in the nucleus accumbens and this effect was counteracted by GABA blockers. These findings suggest that modafinil suppresses the release of GABA, which in turn facilitates the release of dopamine. Evidence supporting enhanced GABA release is an important aspect of this research because increased dopamine may account for some of the activity-enhancing effects of adrafinil. In addition, an increase in dopamine may account for the evidence that indicates that modafinil can have positive reinforcing actions (31).

The work summarized thus far indicates that modafinil has widespread CNS effects on GABA release but does not provide evidence about its underlying mechanisms. A direct effect of modafinil on GABA-producing neurons can probably be ruled out. Tanganelli et al. (57) were unable to demonstrate that modafinil causes a decrease in GABA release from cortical slices. Ferraro et al. (27) found that modafinil has no effect on GABA release in both the thalamus and hippocampus. The possibility that modafinil has an indirect effect on GABA release is further supported by evidence that ketanserin, a selective 5-HT₂ antagonist, can suppress the effect of modafinil on GABA release (57).

Less evidence is available about the effect of modafinil on glutamate. Generally, research suggests that glutamate release is enhanced. Modafinil has been shown to increase glutamate release in the ventro-medial and lateral thalamus, hippocampus (27), and striatum (28).

Effect on Brain Metabolism

A final possible mechanism is that adrafinil is not directly linked to any particular neurotransmitter system, but rather it has a more general effect on brain metabolic rate. Touret et al. (58) found increased levels of glutamine synthetase in rats in both, the locus coeruleus and cortex, following injection with a high dose of modafinil (128 mg/kg); treatment at 64 mg/kg was ineffective. Glutamine synthetase is synthesized in astrocytes and catabolizes the synthesis of glutamine from glutamate. In the CNS, glutamate is both an energy substrate and a neurotransmitter. Evidence for a role of modafinil in energy metabolism is not restricted to the effect on glutamate. Piérard et al. (46) found that modafinil induced increases in other enzyme systems as well, which resulted in higher levels of aspartate and the creatine-phosphocreatine pool.

Neuroanatomical Specificity

Lin et al. (39) expressed the protooncogene c-Fos and used it as an experimental marker of functional activity to compare the response in cats to amphetamine, methylphenidate, or modafinil at dose levels sufficient to induce wakefulness. Both amphetamine and methylphenidate evoked elevated fos-like immunoreactivity in the striatum and neocortex, most notably in the caudate nucleus and mediofrontal cortex. These observations were not surprising because both regions have high concentrations of dopamine receptors. By contrast, modafinil produced little labeling in either of these structures but induced labeling in the anterior hypothalamic area and in neighboring structures.

Engber et al. (23) also used c-Fos expression to compare the CNS response of amphetamine and modafinil in rats. Modafinil and amphetamine induced c-Fos immunoreactivity in the paraventricular nucleus of the hypothalamus, the anterior hypothalamus, and the central nucleus of the amygdala. Modafinil also affected the suprachiasmatic nucleus, while amphetamine had no effect there. Amphetamine also affected other brain regions where modafinil was without effect.

Collectively, these findings indicate that the regions affected by modafinil are largely restricted to the diencephalon and ventral forebrain. Furthermore, the areas most strongly affected by modafinil are distinct from the regions targeted by amphetamine.

In summary, adrafinil and modafinil have a variety of CNS effects. These include activation of α_1 -adrenergic receptors, release of both GABA and glutamate, and production of a generalized increase in brain metabolism. All of these effects can be linked to an increase in glutamate synthesis and/or release. First, glutamate generally functions as an excitatory neurotransmitter and could, therefore, mediate activation by adrafinil of other CNS transmitter systems. Glutaminergic activation of the noradrenergic system could explain the data suggesting α_1 -adrenergic agonist activity in the CNS but not in the peripheral nervous system. Glutamate also activates the serotonergic system, which has inhibitory effects on GABA release. The glutamate hypothesis can account also for the evidence that modafinil generally decreases release of GABA. Glutamate is the precursor GABA in GABAergic neurons — consequently, the greater the glutamate release, the less glutamate is available for synthesis of GABA. Glutamate is also involved in energy metabolism, which could represent a link between adrafinil and metabolism.

The above suggestions remain speculative; no evidence linking adrafinil or modafinil to specific receptors that influence glutamate release is known. More receptor binding studies are clearly needed. Another intriguing result is the apparent anatomical selectivity of the actions of modafinil. These observations provide the greatest challenge to a glutaminergic hypothesis in view of the ubiquitous presence of glutamate as an excitatory neurotransmitter.

Neuroprotective Effects

Evidence that amphetamine can promote recovery of function following brain injury prompted Fuxe et al. (30) to examine the effects of modafinil on degenerative processes

induced by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the mouse. They found that MPTP-induced dopamine cell loss in the striatum was markedly reduced by chronic treatment with modafinil, even at the low dose of 10 mg/kg. A significant but smaller decrease occurred when modafinil was administered only once. The maximum effectiveness of modafinil was when it was administered before or shortly after treatment with MPTP. No neuroprotective effects were observed when the treatment was delayed by 3 h. The authors also found greater neuroprotective effects in the striatum than in the substantia nigra. Two possible processes may contribute to these findings: modafinil prevented cell death; and it had neurotrophic effects that promoted additional growth. These authors raise the possibility that neuroprotective effects resulted from reduced GABA release.

Two additional studies using other models of brain dopamine disruption have confirmed the neuroprotective effects of modafinil (59,60). Ueki et al. (60) looked at the effect of modafinil treatment in rats after receiving unilateral transections of the nigrostriatal pathway. Compared to controls, animals treated with 100 mg/kg of modafinil showed less depletion of dopamine and greater staining of tyrosine hydroxylase. These neuroprotective effects were not limited to brain dopamine systems; serotonergic and noradrenergic systems were also affected. They also obtained behavioral evidence of neuroprotection. Animals administered apomorphine following unilateral lesions showed circling (rotational behavior) in the direction of the lesioned side. This ipsilateral rotational behavior was markedly reduced by modafinil. The second study (59) showed that modafinil was able to partially counteract both the morphological and behavioral deficits of ischemic lesions caused by injection of endothelin-1 into the striatum.

CLINICAL TRIALS

Both adrafinil and modafinil have been the focus of several clinical studies. The majority of studies on modafinil have evaluated its use in patients with sleep disorders, such as narcolepsy, and will not be reviewed here (38,43,61). Most of the clinical studies with adrafinil have looked at its efficacy in treating problems associated with deficits in vigilance. The effects of adrafinil on motor organization and depression have also been examined.

Disorders of Vigilance

As a focus of clinical studies, vigilance has been of greater concern in France than North America. This review will focus on six published studies, all of which were conducted in France and published in French. The subjects examined in these studies were typically outpatients aged 45 years or older with problems in focusing attention, sleep, memory, and mild depression. Subjects were excluded if they showed significant mental deterioration or major psychiatric disorders, such as depression or anxiety. To date, no studies have examined the efficacy of adrafinil in patients with disorders associated with

obvious neuropathology. In fact, dementia and major psychiatric disorders provide specific grounds for exclusion in every study.

1. Israel et al. (35) examined the effects of adrafinil in ambulatory patients, aged 65 years or older, with problems in vigilance of sufficient severity to affect normal daily activities in a double-blind placebo-controlled study. The behavioral syndrome also consisted of moderate depression and loss of general motivation. The final analysis was based on 49 subjects in the placebo group and 50 subjects treated with adrafinil (3 tablets daily) over a 90-day period. Evaluations were made by general practitioners at baseline and days 45 and 90 using a series of tests that included the MacNair scale, the Dynamic Intellect scale, two questionnaires evaluating well-being, and the Sleep Intake Questionnaire from Duke University. The patients were also given a set of psychometric tests at baseline and day 90 to provide a measure of fluidity of cognitive function.

The results showed marked improvements on the Dynamic Intellect Scale measures of confusion, attention, concentration, power of recall, forgetting, vigilance, and fatigue in the adrafinil group. These improvements were generally established by day 45, and in many instances further improvement was seen at day 90. The patients in the adrafinil group also felt happier, more energetic, and less sleepy by the end of the 3 months. In addition, the psychometric tests demonstrated a therapeutic efficacy of adrafinil on vigilance, perceptual acuity, and memory. Three subjects had to have their treatment interrupted during the study because of nausea and dizziness. However, two of the three subjects were in the placebo-controlled group. Two subjects in the adrafinil group experienced light excitation but did not need to terminate treatment.

2. In an open trial, Kohler and Lubin (37) examined the effects of adrafinil in 304 patients, aged 45 to 88 years, who presented with difficulties in attention-concentration, affective troubles, and manifestations of depression. They also displayed problems with memory, anxiety, inactivity, and sleep. The patients received 900 mg/d of adrafinil (600 mg in the morning and 300 mg at noon) for 3 months. Evaluations were made by general practitioners at baseline and days 30 and 90 using Zazzo's test, which provides measures of vigilance, attention, concentration and perceptual-motor skills, Derouesne's scale, which assesses difficulties of daily life, and Zung's Depression and Anxiety scales. They found statistically significant improvements in all three measures, which was apparent within the first month of treatment and persisted for the duration of the study. This study specifically revealed improvements in vigilance, attention, and concentration. Daily activities improved with adrafinil treatment, which reflects improved memory functions and autonomy. Finally, adrafinil treatment resulted in improvements in the degree of depression and anxiety. No secondary effects were observed during the course of this study.

3. Dewailly et al. (18) studied adrafinil in 86 hospitalized patients presenting with troubles of wakefulness or vigilance in a multicenter, double-blind, placebo-controlled study carried out at six hospitals. The SCAG scale revealed improvements in cognitive and relational troubles by day 30, which were maintained until day 60. The Nurse's Observation Scale for Inpatient Evaluation (NOSIE) showed that patients taking adrafinil were less depressed, less irritable, more patient, more sociable, more interested in their surroundings, more communicative, and adapted more easily to the hospital setting. In some instances, these improvements were observed as early as day 15. One subject was reported to show increased aggressiveness by day 15 of treatment, but the subject was in the

placebo group. One subject in the adrafinil group exhibited choreiform movements along with dyskinesia; treatment had to be stopped and restarted.

4. Boyer et al. (7) compared the effect of adrafinil with placebo controls in subjects aged 45–79 years who complained of problems with attention, concentration, memory and orientation. The analysis was based on a total of 548 patients randomized into two treatment groups. Adrafinil treatment resulted in highly significant improvements in daily activities, attention, orientation, and memory. There was no mention of secondary effects in this study.

5. Defrance et al. (16) conducted a multicenter, placebo-controlled study of 49 patients aged 65 years or older from three different hospitals. Twenty-three subjects received adrafinil, while 26 subjects were given placebo. Each of the subjects was hospitalized for at least 1 month with deficits in wakefulness and vigilance. Treatment was most effective in the patients at Center 1. Since these patients were on the average 10 years younger than the patients in the other center, the researchers concluded that this study justified early treatment with adrafinil (i.e., before any cognitive deterioration began). No side effects were observed in the placebo group. Three of the adrafinil treated subjects were reported to show increased agitation and aggression. In one case, the daily dose had to be reduced.

6. Finally, Fontan et al. (29) found significant improvements in self-evaluations of vigilance and sleep in a multicenter, double-blind, placebo-controlled study. The 48 subjects were patients in senior residences, aged 65 years or older, and displayed troubles of vigilance and wakefulness. The subjects had difficulties in attention, concentration, ideation, and a lowered speed to learn and process information. Again, however, subjects were excluded if they had low MMSE scores (< 20). Half of the subjects were treated with adrafinil and half of the subjects were in the placebo-controlled group. The researchers found that adrafinil improved attention and concentration. They also found significant improvements on psychometric tests involving visual masking and reaction time. Performance on the Stroop test was not modified. According to the authors, the most improved factor was immediate mental apprehension of information. Two subjects receiving adrafinil experienced dryness of the mouth, while one placebo subject experienced a bitter taste.

The collective results of all of these studies show an impressive degree of consistency; they indicate that adrafinil can be highly beneficial in the treatment of elderly patients showing deficits in vigilance, attention, behavior, and mood.

Deficits Associated with Motor Organization

Boyer et al. (8) examined the effect of adrafinil on ideomotor deficits, which included general suppression in voluntary movements, deficits in organizing motor sequences, paralysis of decision, and paralysis of functional motor action. A total of 81 subjects participated in a multicenter, placebo-controlled study. None of the patients were institutionalized.

The treatment consisted of adrafinil 600 mg/d (300 mg in the morning and 300 mg at noon) or placebo for 28 days. Evaluations were made at baseline and on days 7 and 28. The AMDP system (4th and 5th scale), General Somatic and Psychopathological Scale,

Motor Activity Scale, Sheehan Scale of Social Incapacitation (anxiety), Visual Analogic Scales, and 3 global instruments [efficacy, tolerance and the Clinicians Global Impression (CGI) index] were used as the evaluation tools.

Adrafinil treatment resulted in significant improvements in 3 factors of the AMDP system: depression, apathy-retardation, and somatic symptoms. The paralysis of motor action and the 3 components of the Sheehan scale were significant in the adrafinil group, confirming the possibility of a reorganization of action. The analysis of the factors of change under adrafinil confirmed the existence of the first factor of change in the adrafinil group. This factor consists of the global score of the CGI index, the 3 components of the Sheehan scale, the 4 types of inhibition of action, the total score of the Motor Activity scale, the score of the Visual Analogic scale of motor activity, and the anxiety, depression and neurovegetative scales of the AMDP. Handicap tied to troubles of action, mood, motor, and social interactions is a general factor of change. This factor of change was not found in the placebo group. The researchers concluded that adrafinil has therapeutic efficacy on ideomotor deficits, which is independent of diagnostic category. Two subjects in the adrafinil group were removed from the study due to nausea and arrhythmia. One subject in the placebo group was removed because of somnolence.

Treatment of Depression

Mild behavioral depression was a common characteristic of many of the subjects studied in the vigilance-promoting studies described previously. The term "depression" does not refer to the clinical syndrome as defined in DSM-IV but rather to a milder type of depression that is common in the elderly.

The clinical effect of adrafinil on depression was the focus of a study by Guyotat (32). Adrafinil (600 mg/d) was compared to clomipramine (40 mg/d) and placebo in a group of 70 depressed patients over a 2-mo period. Clinical efficacy was evaluated using conventional rating scales: the Hamilton Depression Rating scale, Psychomotor Retardation, Raskin Depression scale, and COVI-Anxiety scale. Statistically significant improvements in depression were obtained for both adrafinil and clomipramine when compared to placebo. Adrafinil, however, also had a higher efficacy on psychomotor retardation than clomipramine. The clomipramine group suffered from frequent side effects (50% of patients), while adrafinil was well tolerated. In the placebo group, undesirable effects (somatic or psychological) were observed in 25% of the subjects (e.g., tremors, dry mouth, stomach pain, agitation). Secondary effects were less noticeable in the adrafinil group, although they were reported to exhibit a transient period of psychological agitation and irritability.

SUMMARY AND CONCLUSIONS

Adrafinil is a novel drug that is not well known outside of France, where it is used primarily as a vigilance-enhancing agent. Clinical studies strongly indicate that adrafinil has

efficacy in improving attention, memory, as well as other deficits resulting from decreased vigilance.

Adrafinil has two metabolites, modafinil and CRL 40476. Little is known about CRL 40476. Modafinil, on the other hand, has been much more extensively studied, and the production of modafinil is likely to account for at least part of the effects of adrafinil. Thus, adrafinil has very similar pharmacological effects to modafinil. Moreover, the behavioral effects of adrafinil are more closely tied to the pharmacokinetics of its metabolite modafinil.

Most researchers assume that adrafinil works as a selective α_1 -adrenergic receptor agonist. This belief, however, is challenged by evidence that adrafinil does not produce peripheral adrenergic effects, instances where the actions of adrafinil are not blocked by α_1 blockers, and by instances where adrafinil is unable to counteract the effect of α_1 blockers. Recent evidence indicates that adrafinil affects amino acid release, generally causing increased release of glutamate and decreased release of GABA.

Given the effectiveness of adrafinil in improving performance on psychometric tests and motor function in people with mild cognitive impairment, it is surprising that neither adrafinil nor modafinil have been used in trials with demented patients. In fact, two possible applications deserve careful consideration. One possible application is the treatment of age-associated memory impairment (AAMI). This term was introduced to describe "medically, neurologically, and psychiatrically healthy persons over 50 years of age who have experienced a gradual decline in the ability to perform certain tasks of daily life dependent on memory" (14,15).

A second possible application for adrafinil would be in the treatment of subjects with dementing disorders, such as Alzheimer's disease. This application is not directly suggested from the studies performed thus far, which have precluded examination of severely demented patients because of the subject selection criterion used. In fact, research with canines provides limited support for this possibility. Adrafinil improved discrimination learning in a group of aged dogs; the dogs that showed the greatest improvement in cognitive functioning were those that showed the greatest overall impairment (42).

The evidence that modafinil can have neuroprotective effects provides another compelling reason for testing adrafinil in patients with dementing disorders. This study raises at least the possibility that long-term treatment with adrafinil can arrest or even reverse neurodegenerative processes that contribute to dementia. Clearly, however, further preclinical studies are needed before this potential application can be evaluated.

Three other therapeutic applications of adrafinil warrant further study. The first application is as a potential therapeutic drug in treatment of Parkinson's (see ref. 30) and another is as a potential treatment for deficits associated with movement disorders (8). Finally, further investigations of the antidepressive effects of adrafinil are warranted.

In summary, adrafinil is a novel stimulant that lacks the adverse effects associated with other psychostimulants. It directly affects CNS function, but its mechanism of action is not completely understood. Clinical studies have demonstrated that adrafinil has efficacy as a vigilance-promoting agent. It has also cognitive enhancing potential, and trials on patients with dementing disorders appear warranted.

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