DOPAMINERGIC–ADRENERGIC INTERACTIONS IN THE WAKE PROMOTING MECHANISM OF MODAFINIL

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Abstract—Adrenergic signaling regulates the timing of sleep states and sleep state-dependent changes in muscle tone. Recent studies indicate a possible role for noradrenergic transmission in the wake-promoting action of modafinil, a widely used agent for the treatment of excessive sleepiness. We now report that noradrenergic projections from the locus coeruleus to the forebrain are not necessary for the wake-promoting action of modafinil. The efficacy of modafinil was maintained after treatment of C57BL/6 mice with N-(2-chloroethyl)-N-ethyl 2-bromobenzylamine (DSP-4), which eliminates all noradrenergic transporter-bearing forebrain noradrenergic projections. However, the necessity for adrenergic receptors in the wake-promoting action of modafinil was demonstrated by the observation that the adrenergic antagonist terazosin suppressed the response to modafinil in DSP-4 treated mice. The wake-promoting efficacy of modafinil was also blunted by the dopamine autoreceptor agonist quinpirole. These findings implicate non-noradrenergic, dopamine-dependent adrenergic signaling in the wake-promoting mechanism of modafinil. The anatomical specificity of these dopaminergic–adrenergic interactions, which are present in forebrain areas that regulate sleep timing but not in brain stem areas that regulate sleep state-dependent changes in muscle tone, may explain why modafinil effectively treats excessive daytime sleepiness in narcolepsy but fails to prevent the loss of muscle tone that occurs in narcoleptic patients during cataplexy. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: modafinil, noradrenaline, dopamine, dopamine transporter, cataplexy, DSP-4.

Adrenergic signaling in the CNS plays a prominent role in the timing of sleep states and in regulating sleep-dependent physiological and behavioral phenomena (Siegel, 2000; Aston-Jones et al., 2001; Berridge and Waterhouse, 2003). The noradrenergic locus coeruleus (LC) is one of the aminergic nuclei that exhibit robustly sleep state-dependent firing patterns (Aston-Jones and Bloom, 1981; Jouvet, 1966). The LC serves as the source of noradrenergic neurotransmission in the forebrain and has been implicated in the timing of sleep states (McCormick, 1992; McCormick et al., 1999) and histaminergic tuberomammillary nuclei (TMN; Steininger et al., 1999), exhibit high activity during wake, dramatically reduced activity during non-rapid-eye-movement sleep (NREMS), and nearly complete inactivity during rapid-eye-movement sleep (REMS). The terminal projections of LC neurons lie in close apposition to neurons expressing adrenergic receptors, and adrenergically innervated areas such as the basal forebrain and thalamus are implicated in the timing of sleep states (McCormick, 1992; Siegel, 2000; Berridge et al., 2003). The wake-promoting effect of noradrenaline (NA) has been amply demonstrated in many experiments. Thus, α1 adrenergic agonists promote wakefulness, in part by potentiating the activity of cortically projecting neurons of the basal forebrain (Berridge et al., 2003). By contrast, activation of inhibitory α2 adrenergic receptors, which are located presynaptically on noradrenergic and other axons, induces profound sedation (Aghajanian and VanderMaalen, 1982; Nelson et al., 2003). In narcoleptic dogs the occurrence of cataplexy, a state of muscle atonia akin to that of REMS, is associated with cessation of firing of LC neurons (Wu et al., 1999). Cataplexy is treated most effectively with agents that either stimulate α1 receptors directly (Mignot et al., 1993; Nishino et al., 1993) or increase noradrenergic tone by blocking the reuptake of extracellular NA by the cell membrane NA transporter (NAT; Foutz et al., 1981). Together, these data indicate that LC noradrenergic neurons play a role in sustaining the waking state and in maintaining muscle tone during waking.

Adrenergic transmission is an attractive target for the development of wake-promoting therapeutics, and there is considerable pharmacological evidence that the most widely prescribed wake-promoting agent, modafinil, acts through adrenergic mechanisms to promote waking (Duteil et al., 1990; Lin et al., 1992; Stone et al., 2002a). This contention is also supported by the recent observation that modafinil potentiates noradrenergic inhibition of the sleep-active neurons of the ventrolateral preoptic area of the hypothalamus in vitro (Gallopin et al., 2004). Conversely, other data, including the competitive binding of modafinil to the dopamine (DA) transporter (DAT) in vitro (Mignot et al., 1994) and the failure of modafinil to induce wakefulness in mice lacking the DAT (Wisor et al., 2001), implicate dopaminergic transmission in the wake-promoting mechanism of modafinil.

There is a complex relationship between brain dopaminergic and adrenergic signaling systems: DA is the biochemical precursor of NA and may be a physiological

Wu et al., 1999; Siegel, 2000). These nuclei, which also include the serotoninergic raphe (McGinty and Harper, 1976) and histaminergic tuberomammillary nuclei (TMN; Steininger et al., 1993), exhibit high activity during wake, dramatically reduced activity during non-rapid-eye-movement sleep (NREMS), and nearly complete inactivity during rapid-eye-movement sleep (REMS). The terminal projections of LC neurons lie in close apposition to neurons expressing adrenergic receptors, and adrenergically innervated areas such as the basal forebrain and thalamus are implicated in the timing of sleep states (McCormick, 1992; Siegel, 2000; Berridge et al., 2003). The wake-promoting effect of noradrenaline (NA) has been amply demonstrated in many experiments. Thus, α1 adrenergic agonists promote wakefulness, in part by potentiating the activity of cortically projecting neurons of the basal forebrain (Berridge et al., 2003). By contrast, activation of inhibitory α2 adrenergic receptors, which are located presynaptically on noradrenergic and other axons, induces profound sedation (Aghajanian and VanderMaalen, 1982; Nelson et al., 2003). In narcoleptic dogs the occurrence of cataplexy, a state of muscle atonia akin to that of REMS, is associated with cessation of firing of LC neurons (Wu et al., 1999). Cataplexy is treated most effectively with agents that either stimulate α1 receptors directly (Mignot et al., 1993; Nishino et al., 1993) or increase noradrenergic tone by blocking the reuptake of extracellular NA by the cell membrane NA transporter (NAT; Foutz et al., 1981). Together, these data indicate that LC noradrenergic neurons play a role in sustaining the waking state and in maintaining muscle tone during waking.

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ligand of adrenergic receptors (Zhang et al., 2004) and a substrate for NAT (Giros et al., 1994). Interactions between the dopaminergic and noradrenergic transmitter systems have hampered attempts to elucidate the exact target for the wake-promoting effect of modafinil. It is possible to delineate functions mediated by NA and DA using the NA-specific neurotoxin N-(2-chloroethyl)-N-ethyl 2-bromobenzylamine (DSP-4). This toxin ablates NAT-bearing noradrenergic neurons and post-synaptic dopaminergic and adrenergic targets intact (Monti et al., 1988; Fritschi and Grzanna, 1991). In this study, we utilized DSP-4 treatment and subsequent administration of adrenergic and dopaminergic agents to demonstrate that interactions of dopaminergic and adrenergic signaling mechanisms contribute to the wake-promoting effect of modafinil in vivo.

**EXPERIMENTAL PROCEDURES**

**Surgery and experimental setting**

Male 8–10 weeks-old C57BL/6 mice (Jackson Laboratories, Bar Harbor, ME, USA) were anesthetized with isoflurane and surgically prepared for electroencephalographic (EEG) and electromyographic (EMG) recordings as described elsewhere (Edgar and Seidel, 1997; Wisor et al., 2001). Following recovery, mice were maintained under 12-h light/dark (LD12:12) cycles within separate compartments of a sound-attenuated stainless steel recording chamber with food and water available ad libitum for 4 days prior to experimentation. All experimental procedures were performed in AAALAC-approved facilities in compliance with institutional and National Institutes of Health guidelines for treatment of experimental animals. All efforts were made to minimize animal suffering or discomfort and to reduce the number of animals used. EEG was digitized at 100 Hz with 1–30 Hz band pass and EMG was integrated with 10–100 Hz band pass in 10-s epochs, which were classified as wake, REMS, or NREMS by visual inspection.

**Experiment 1: effect of DSP-4 on the response to nisoxetine and modafinil**

A 24-hour baseline recording of EEG and EMG was initiated at the onset of light (Zeitgeber time [ZT] 0). Parallel groups were then treated with either the NAT blocker nisoxetine (2 mg/kg) and vehicle (n=16) or modafinil and vehicle (n=13) in a repeated measures design. The two injections were administered at ZT6 and separated by 48 h. The order of treatments was randomized individually for each mouse. On the day after the second of these two injections, all mice received two injections of DSP-4 (50 mg/kg) separated by 96 h. Seven days later baseline recordings of EEG and EMG were initiated at ZT0, and mice were then subjected to the same treatments (nisoxetine and vehicle, or modafinil and vehicle) as they had received prior to DSP-4 treatment.

**Experiment 2: effects of pharmacological pre-treatments on the response to modafinil**

Mice that had been subjected to nisoxetine and DSP-4 in experiment 1 (n=16) were subsequently given six additional treatments. These treatments started 48 h after the end of experiment 1 and were administered at ZT6 at 48 h intervals. Each treatment consisted of paired injections separated by 10–15 min. The six paired injections were: vehicle–handling, vehicle–modafinil, terazosin–vehicle, terazosin–modafinil, quinpirole–vehicle and quinpirole–modafinil and were given in a randomized order for each subject. Subsequently, these mice were killed and perfused for immunohistochemistry along with untreated control mice.

**Drugs**

The NAT blocker nisoxetine (2 mg/kg; Python et al., 1997), modafinil (90 mg/kg; Wisor et al., 2001), the DA autoreceptor agonist quinpirole (0.015 mg/kg; Monti et al., 1989) and the α1-adrenergic antagonist terazosin (5 mg/kg; Stone et al., 2002a) were administered at doses previously documented to influence sleep or behavioral measures of wakefulness. All drugs were purchased from Sigma-Aldrich (St. Louis, MO, USA) and were administered intraperitoneally in 0.25% methylcellulose/0.9% saline vehicle. Modafinil was delivered in suspension. All other compounds were in solution.

**DA β-hydroxylase (DβH) immunohistochemistry**

Mice (six DSP-4 treated, four controls) were perfused transcardially with cold 4% paraformaldehyde in 100 mM phosphate buffer (pH 7.4) and the brain was postfixed overnight in the same fixative at 4 °C. After cryoprotection, 30 µm coronal cryosections were cut, and the DSP-4-treated and control sections were then processed in parallel for DβH immunoreactivity. The sections were first incubated in blocking solution composed of 5% normal goat serum and 0.2% bovine serum albumin dissolved in PBS with 0.3% NiCl, and 0.015% H2O2 dissolved in Tris–HCl (Sigma), 0.1% NtCl, and 0.015% H2O2 dissolved in Tris–HCl (pH 7.6).

**RESULTS**

**Effect of DSP-4 on spontaneous sleep and the response to nisoxetine**

Seven days after DSP-4 treatment, neither NREMS nor REMS as a percentage of the 24-h observation period was changed from pre-DSP-4 baseline levels. Sleep predomi-
nated during the light portion of the LD12:12 cycle and wake during the dark portion (Fig. 1A, B). Immunostaining for DβH/H9252 confirmed the efficacy of the DSP-4 treatment; regions that receive most of their adrenergic innervation from the LC, such as the hippocampus and much of the cerebral cortex (e.g. motor cortex; Fig. 1C, D) exhibited a greatly reduced density of DβH-stained axons.

The efficacy of the DSP-4 lesion was also measured pharmacologically by assessment of the REMS suppressing effect of the NAT blocker nisoxetine before and after DSP-4 treatment (Fig. 2). The latency to sleep after nisoxetine administration was not significantly greater before (20±3 min) or after (21±2 min) DSP-4 treatment as compared with vehicle (26±3 min before and 25±4 min after DSP-4). Prior to DSP-4, however, nisoxetine suppressed REMS by approximately 50% (Fig. 2A) while leaving NREMS intact (Fig. 2C). REMS as a percentage of the first hour of accumulated sleep was significantly lower after nisoxetine than after vehicle prior to DSP-4 treatment (Fig. 2E).

After DSP-4 lesion, the REMS suppressing effect of nisoxetine was abolished (Fig. 2B, E). ANOVA confirmed a significant DSP-4 lesion × nisoxetine treatment interaction [F(1,15)=5.91, P=0.028]. Thus, DSP-4 treatment de-
Subsequent to DSP-4 treatment, the wake-promoting efficacy of modafinil was intact; modafinil still increased the latency to sleep approximately five-fold (Fig. 3E). While ANOVA indicated a significant effect of modafinil administration \( F_{1,12} = 14.758, P = 0.002 \), neither DSP-4 treatment nor DSP-4 × modafinil interaction was significant \( P > 0.5 \). This observation demonstrated that LC forebrain terminals are not necessary for the wake-promoting efficacy of modafinil.

**Effects of terazosin and quinpirole on the response to modafinil in DSP-4-treated mice**

Modafinil injection preceded by vehicle treatment suppressed both NREMS and REMS (Fig. 4A, B), and resulted in a 4.5-fold increase in the latency to sleep relative to vehicle alone (Fig. 4C), a magnitude similar to the previously observed effect of modafinil (Fig. 3E). Quinpirole pretreatment attenuated the wake-promoting effect of modafinil: the modafinil-induced decrease in NREMS as a percentage of time was significantly attenuated and the increase in sleep latency was abolished by quinpirole treatment (Fig. 4A, C). The increased latency to the accumulation of 1 h of sleep after modafinil injection was also significantly blunted by quinpirole treatment (Fig. 4D). Similar to quinpirole, terazosin pre-treatment prior to modafinil injection attenuated the wake-promoting effect of modafinil (Fig. 4A). The modafinil-induced increase in sleep latency (Fig. 4C) was abolished, and the latency to the accumulation of 1 h of sleep attenuated, by terazosin (Fig. 4D). These results demonstrate that the wake-promoting effect of modafinil can be attenuated either by suppression of DA release or by prevention of \( \alpha_1 \) receptor activation.

**DISCUSSION**

In the two decades since the discovery of its robust wake-promoting effect, modafinil has become the most widely used prescription drug for treatment of excessive sleepiness. Yet to date, the mechanism by which modafinil produces sustained waking remains controversial (Saper and Scammell, 2004). Effects on both noradrenergic (Duteil et al., 1990; Lin et al., 1992; Stone et al., 2002a; Gallopin et al., 2004) and dopaminergic (Mignot et al., 1994; Nishino et al., 1998; Wisor et al., 2001) transmission have been hypothesized to mediate the wake-promoting effect of this compound.

A wealth of pharmacological data demonstrates the necessity for adrenergic receptors in the response to modafinil. The wake-promoting effect of modafinil in cats (Lin et al., 1992), monkeys (Duteil et al., 1990; Hermant et al., 1991) and mice (Duteil et al., 1990; and the current report) is blocked by \( \alpha_1 \) antagonists, but not by postsynaptic DA receptor antagonists (Lin et al., 1992). Likewise, nonspecific \( \alpha \)-adrenergic antagonists (but not 1a- or 1d-specific antagonists; Stone et al., 2002a) blunt the behavioral activating effect of modafinil in mice, and mice lacking the \( \alpha_1b \) receptor due to genetic inactivation exhibit reduced sensitivity to modafinil (Stone et al., 2002a). Stress, which downregulates \( \alpha_1 \) adrenergic receptors in the brain,
does not alter the response to dopaminergic agents, but does reduce the efficacy of modafinil (Stone et al., 2002b). At the physiological level, modafinil and the α1 blocker prazosin act antagonistically to desynchronize and synchronize, respectively, the cortical EEG (Sebban et al., 1999). Taken together, these data strongly suggest that modafinil promotes waking by activating α1 adrenergic receptors. Furthermore, in a recent in vitro electrophysiological study, modafinil had similar effects to those of the NAT blocker nisoxetine (Gallopín et al., 2004), which led to the hypothesis that modafinil promotes wakefulness by elevating extracellular NA concentration via NAT blockade.

If NAT is critical for the wake-promoting efficacy of modafinil, destruction of NAT-bearing terminals should abolish or at least attenuate the response to modafinil. We addressed this hypothesis by treating mice with DSP-4, which destroys NAT-bearing forebrain NA terminals. Both the absence of a nisoxetine effect and the lack of DBH immunoreactive axons in the forebrain demonstrated that the toxin had caused the expected damage to LC noradrenergic axons. In this condition, the robust wake-promoting effect of modafinil was intact, which shows that these projections are not necessary for the wake-promoting action of modafinil.

Fig. 4. Quinpirole and terazosin pre-treatments block the wake-promoting effects of modafinil in DSP-4 treated mice (n=16). (A, B) NREMS (A) and REMS (B) as a percentage of time in 30-min bins in the 4 h subsequent to modafinil with vehicle pretreatment (white triangles), quinpirole pre-treatment (black circles), terazosin pre-treatment (black triangles), or subsequent to vehicle alone (white circles). (C) Latency to the occurrence of a 1-min bout of sleep subsequent to the second of two paired injections. (D) Latency to the occurrence of 1 h of sleep subsequent to the second of two paired injections. * P<0.05 vs. modafinil treatment. # P<0.05 vs. vehicle treatment.
The failure of DSP-4 administration to alter baseline sleep is consistent with some previous studies (Cirelli and Tononi, 2004), and may reflect the fact that other monoaminergic cell groups, including sparse noradrenergic fibers originating from cells outside the LC that are devoid of NAT (Fritschy and Grzanna, 1991), remain intact. REMS has been reported to exhibit a sustained decrease (Gonzalez et al., 1998), to acutely decrease and subsequently increase (Monti et al., 1988), or not change at all (Cirelli and Tononi, 2004) in the days after DSP-4 treatment. Similarly, wake as a percentage of time has been reported to decrease then return to baseline values (Gonzalez et al., 1998) or to not change at all (Cirelli and Tononi, 2004). These conflicting reports reflect, in part, the timing of sleep studies relative to DSP-4 injection, but also may be a consequence of species or strain differences in the timing of DSP-4-induced LC degeneration, which is a protracted process (Fritschy et al., 1990), or in the pace and magnitude of changes in cerebral gene expression (Cirelli and Tononi, 2004) or noradrenergic receptor function (Monti et al., 1988) that occur as a result of DSP-4 treatment. In view of the fact that DSP-4 attenuates recovery sleep after behaviorally but not pharmacologically induced wake (Gonzalez et al., 1996), it would be informative to determine whether recovery sleep after modafinil-induced wake is modulated by DSP-4 administration; however, in the current study we did not observe sleep for a sufficient period of time after modafinil administration to address this issue.

The necessity of α1 receptors for modafinil-induced arousal (Stone et al., 2002a) and the ability of the α-adrenergic antagonist terazosin to suppress modafinil-induced waking even in DSP-4-lesioned mice, as demonstrated in the current study, might suggest that modafinil is a direct α-adrenergic agonist. Yet modafinil does not bind to adrenergic receptors at physiologically relevant concentrations (Mignot et al., 1994), and in the in vitro study mentioned above, in which adrenergic receptor activation by NA caused suppression of sleep active neurons, modafinil had no direct adrenergic effect in the absence of NA even at a high dose (Gallopin et al., 2004). Furthermore, modafinil does not suppress cataplexy in narcoleptic dogs and humans (Billiard et al., 1994; Shelton et al., 1995), while both α-adrenergic agonists, particularly α1b agonists, and NAT blockers do (Mignot et al., 1993; Nishino et al., 1993). Thus, it is unlikely that modafinil activates any of the known adrenergic receptors.

There is considerable evidence that modafinil induces wake by blocking the clearance of DA from the extracellular milieu. The cell membrane DAT is the only documented binding site for modafinil in the CNS (Mignot et al., 1994), and animals lacking this transporter do not exhibit modafinil-induced wakefulness (Wisor et al., 2001). Modafinil increases the extracellular concentration of DA in the cerebral cortex (de Saint Hilaire et al., 2001) and in the caudate (Wisor et al., 2001), as would be expected for a compound that inhibits the activity of the DAT. Furthermore, the in vivo potencies of modafinil and other wake-promoting agents are correlated with their affinities to DAT, and not to NAT (Nishino et al., 1998).

The efficacy of modafinil is determined in part by pre-synaptic influences on dopaminergic transmission but not by postsynaptic DA receptors (Lin et al., 1992). In this report, the prevention of modafinil-induced sustained wake by the DA autoreceptor agonist quinpirole provides pharmacological verification of this relationship. It should be noted that while modafinil failed to induce sustained wake in the presence of either quinpirole or terazosin, neither pre-treatment blocks completely the effects of modafinil on sleep. Partial suppression of NREMS, and complete suppression of REMS, by modafinil was still observed. Why the suppression of REMS by modafinil is completely intact after quinpirole (or terazosin) pre-treatment cannot be ascertained based on the current data. Given that, in general, REMS is more sensitive than NREMS to disruption by manipulations of catecholaminergic transmission (Nicholson and Pascoe, 1990; Pungor et al., 1993; de Saint Hilaire et al., 1995), it is possible that the suppression of REMS results from a low level of activation of adrenergic and/or dopaminergic receptors in the brain, or even as yet unknown non-catecholaminergic effects of modafinil. Even so, other data provide further support for the role of dopaminergic transmission in response to modafinil. Polymorphisms in the gene encoding catechol-O-methyl transferase, an enzyme necessary for the synthesis of DA, confer variability in the efficacy of modafinil in narcoleptic patients (Dauvilliers et al., 2002). The catecholaminergic neurotoxin 6-hydroxy-DA, which lesions both noradrenergic and dopaminergic cells of the brain, reduces dramatically the suppression of cortical GABA release by modafinil (Tanganelli et al., 1994). Given that NA-specific lesion with DSP-4 did not affect the response to modafinil in the current study, the effect of 6-hydroxy-DA may be attributable to dopaminergic lesion. Together, these observations confirm the dependence of modafinil on DA release in the CNS for its wake-promoting effect.

There is increasing evidence that DA may act as a physiological ligand at adrenergic receptors, and dopaminergic stimulation of adrenergic receptors has been documented in the brain stem (Crochet and Sakai, 2003) the preoptic area (Cornil et al., 2002) and the hippocampus (Malenka and Nicoll, 1986). DA and NA differ in their affinity for α-adrenergic receptors by just two- to three-fold and are nearly equipotent at activating second messenger pathways through α1 adrenergic receptors (Zhang et al., 2004). Therefore, in anatomical areas where dopaminergic projections are present in abundance in close apposition to adrenergic receptors, DA may stimulate adrenergic receptors.

In view of the necessity for DAT-bearing dopaminergic terminals and for adrenergic receptors in the mechanism of modafinil, we propose a model in which dopaminergic and adrenergic cells of the brain, reduces dramatically the suppression of cortical GABA release by modafinil (Tanganelli et al., 1994). Given that NA-specific lesion with DSP-4 did not affect the response to modafinil in the current study, the effect of 6-hydroxy-DA may be attributable to dopaminergic lesion. Together, these observations confirm the dependence of modafinil on DA release in the CNS for its wake-promoting effect.

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by facilitating the activity of wake-related CNS circuitry, by suppressing the activity of NREMS-related CNS circuitry, or both. I.c.v. modafinil elevates extracellular histamine levels in the TMN (indirectly, since infusion of modafinil directly into the TMN does not have this effect; Ishizuka et al., 2003) and s.c. modafinil suppresses cortical GABA release (albeit through a catecholamine-dependent mechanism; Tanganelli et al., 1994, 1995). Modafinil also elevates extracellular glutamate levels in the brain (Ferraro et al., 1998) by mechanisms that appear to be indirect as well (Perez de la Mora et al., 1999). All of these phenomena provide plausible effector mechanisms for modafinil.

The failure of modafinil to suppress cataplexy may stem from the anatomical specificity of DAT expression in the CNS (Hurd et al., 1994; Freed et al., 1995; Freeman et al., 2001). In those areas of the brain where both wake-promoting adrenergic receptors (McCormick, 1992; Berridge et al., 2003; Jones, 2004) and DAT-bearing dopaminergic terminals are present, such as the basal forebrain cholinergic complex, cerebral cortex and thalamus, modafinil increases extracellular DA concentration, resulting in dopaminergic activation of postsynaptic adrenergic receptors. In areas where adrenergic receptors are present and regulate sleep-dependent changes in muscle tone but are not in close apposition to DAT-bearing dopaminergic terminals, such as the basal forebrain cholinergic complex, cerebral cortex and thalamus, modafinil is pharmacologically inactive. The anatomical specificity of dopaminergic–adrenergic interactions thus provides an explanation for the failure of modafinil to prevent cataplexy in narcoleptic patients, even as it suppresses excessive sleepiness. The uniquely robust wake-promoting efficacy of modafinil may reflect in part the exceptionally long half-life of this compound in vivo (12–15 h in humans; Robertson and Hellriegel, 2003), but the mechanism of action proposed here should nonetheless apply to other DAT blockers as well. This claim is supported by the fact that other DAT blockers, such as GBR12909 promote wake but are largely ineffective at suppressing cataplexy in narcoleptic (Mignot et al., 1993).

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