

## Short Note

# Modafinil Binds to the Dopamine Uptake Carrier Site with Low Affinity

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Modafinil is a stimulant compound with an unknown mechanism of action that has been used successfully to control excessive daytime sleepiness in narcoleptic patients in Europe (1,2). The compound also has a minimal effect on cataplexy and other accessory symptoms of the narcolepsy tetrad (1,2). It is well tolerated and is generally preferred to amphetamine and related compounds in the countries where it is available.

The mode of action of modafinil is still not understood. The compound has been shown to decrease sleep and increase wakefulness in cats (3) and monkeys (4), and increase spontaneous locomotion in mice and to a lesser extent in rats (5). It also decreases barbital- and phenobarbital-induced sleep in mice and rats and does not produce stereotypies below very high doses (5). The compound is suggested to have no peripheral effects in rodents, dogs and monkeys (5-7). Surprisingly, the compound is also devoid of any sympathomimetic effects, including those at the cardiovascular level (2,6).

The current hypothesis regarding the mode of action of modafinil involves the stimulation of alpha-1 adrenergic mechanisms. The modafinil-induced increase in motor activity in mice is antagonized by central alpha-1 antagonists such as prazosin or phenoxybenzamine, but not by dopamine antagonists (5). Similarly, the awakening properties of the compound (in monkeys and cats) were antagonized by prazosin, although antagonisms were only partial (3).

Other experiments, however, have suggested a different mode of action. First, the compound does not bind alpha-1 receptors *in vitro* (up to  $10^{-3}$  M using [ $^3$ H]-prazosin in canine cortical membranes, data not shown). Secondly, our experiments in narcoleptic canines have shown that the compound does not modify canine cataplexy even at doses promoting alertness (7). Because canine cataplexy is very sensitive to compounds acting presynaptically and postsynaptically on

adrenergic transmission (see reference 8 for review), the results suggest a nonadrenergic mode of action. Electrophysiological and voltametric data also do not support the hypothesis of catecholaminergic mechanism of action. High doses of modafinil have been shown not to modify the firing rate of noradrenergic neurons of the locus coeruleus or dopaminergic neurons of the ventral tegmental area or substantia nigra in rats (9). Similarly, modafinil does not modify catechol oxidation peaks as measured by voltametry in the mouse caudate nucleus and rat striatum or nucleus accumbens, including after pargyline treatment (10).

To further study the profile of modafinil, the compound was evaluated using the NIMH/Novascreen® Psychotherapeutic Drug Discovery and Development Program. Binding assay experiments included receptors for adenosine, dopamine,  $\gamma$ -aminobutyric acid (GABA), serotonin, *N*-methyl-D-aspartate, kainate, quisqualate, glycine (strychnine sensitive and insensitive), benzodiazepine, phencyclidine (PCP), MK-801, angiotensin, Arg-vasopressin, bombesin, cholecystokinin (central and peripheral), neuropeptide Y (NPY), substance K and P, neurotensin, somatostatin, vasoactive intestinal polypeptide (VIP), atrial natriuretic factor 1 (ANF1), epidermal growth factor, nerve growth factor, various ion channels (calcium channels N, T and L; chloride channels and low conduction potassium channels) and second messenger systems (adenylate cyclase, phorbol ester and inositol triphosphate). All results were negative when a concentration of  $10^{-3}$  M was tested.

In a second set of studies, we decided to explore the affinity of modafinil for various neurotransmitter uptake sites. The concentration tested was  $10^{-4}$  M and uptake sites studied included adenosine ( $^3$ H-nitrobenzylthioinosine in rat cortex), choline ( $^3$ H-choline in rat brain), GABA ( $^3$ H-GABA in rat cortical membranes), dopamine ( $^3$ H-WIN in guinea pig striatum), norepinephrine ( $^3$ H-desmethyylimipramine in rat cortex) and

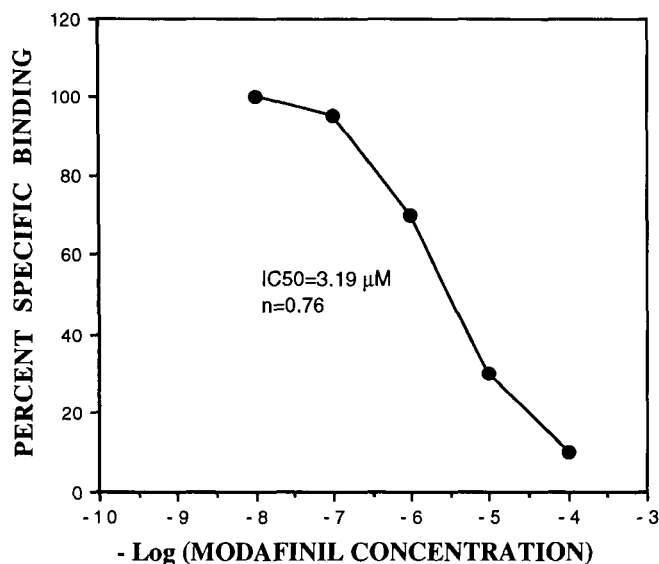


FIG. 1. Competition curve of modafinil against  $^3\text{H}$ -WIN 35,428 in guinea pig striatum. Each point represents the average of duplicate tubes at each of the concentrations tested. For methodological details see Madras et al. (11).

serotonin ( $^3\text{H}$ -citalopram in rat forebrain). No binding inhibition was obtained except for dopamine uptake where 100% inhibition was obtained at  $10^{-4}$  M. A full displacement curve was then performed (Fig. 1) and showed an  $\text{IC}_{50}$  of  $3.19 \times 10^{-6}$  M. The  $\text{KI}$  was  $1.93 \times 10^{-6}$  M (1,930 nM).

In comparison with reference compounds using the same protocol, such as nomifensine (36.9 nM), cocaine (46.2 nM), bupropion (383 nM), clomipramine (3,026 nM) and imipramine (12,900 nM), the activity of modafinil for the uptake site is very weak. The compound is exceptionally selective, however, for the dopaminergic site because it has no affinity on the adrenergic and serotonergic transporters even at a concentration 100 times higher than the  $\text{IC}_{50}$ .

The implication of this property in the psychopharmacological profile of modafinil is unknown. Dopamine uptake inhibition or stimulation of dopamine release is thought to be an important property of most amphetaminelike stimulants, especially for methylphenidate and pemoline (see 8 for references). The very good selectivity of modafinil for the dopaminergic transporter would also explain the relative absence of cardiovascular effects and the lack of anticataplectic properties in narcoleptic canines, more likely to be mediated via adrenergic uptake inhibition (8). On the other hand, it is likely that dopamine uptake inhibition alone does not explain the potency of modafinil as a

stimulant compound. Other selective—and more potent—dopamine uptake inhibitors, such as amineptine or bupropion, are much weaker stimulant compounds in humans. Furthermore, this finding is not in line with previously published studies that demonstrated that modafinil is pharmacologically different from amphetaminelike stimulants (3,5,9,10). It also remains to be examined whether or not the binding of modafinil to the dopamine transporter has any functional effect on dopamine uptake. This is, however, the first report of modafinil binding to a specific receptor. These data may thus stimulate new research directions on the mode of action of modafinil.

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