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## **Modafinil: A Molecule of Military Interest**

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### **ABSTRACT**

Modafinil (Modiodal®) is a synthetic molecule prescribed for the treatment of narcolepsy and idiopathic hypersomnia. It could be used by armed forces for sustained or continuous operations. The waking effect is potent: modafinil allows healthy volunteers to stay awake and efficient for more than 60 hours, without side-effects. The mechanism of action of modafinil is complex, involving the adrenergic system (central  $\alpha$ 1-postsynaptic receptors), associated with serotonergic, GABAergic and probably dopaminergic systems. Moreover, the implication of excitatory amino acids was demonstrated. The anterior hypothalamic nucleus could be the main and specific target for modafinil. It could induce wakefulness by different mechanisms, as compared with other classical vigilance-enhancing drugs such as amphetamines. A neuroprotective effect against neurotoxic organophosphate agents was recently discovered.

Key words: Mechanism of action – Modafinil – Neuroprotection.

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### **INTRODUCTION**

Modafinil (Modiodal®) was introduced in 1994 by the Laboratoire L. Lafon for the treatment of wake disorders such as narcolepsy and idiopathic hypersomnia. Because of its waking properties, low toxicity and absence of tolerance-producing effects, it could be used by armed forces in sustained or

continuous operations involving partial or total sleep deprivation, as in the Gulf War. The pharmacological properties of modafinil are very different from those of the vigilance-enhancing molecule of reference, amphetamine. Its mechanism of action is highly complex and incompletely documented at this time.

The goal of this article is to elucidate the specific mechanism of action of this molecule which does not fit into the classification system of Delay and Deniker and for which a new pharmacological category, “eugregorics” (from *eu*=good and *gregor*=arousal), has been proposed.

### **PHYSICO-CHEMICAL PROPERTIES, PHARMACOKINETICS AND TOXICITY**

Modafinil, or 2-[(diphenylmethyl) sulfinyl] acetamide (Fig. 1), is an active metabolic derivative of adrafinil. Modafinil has proven to be more interesting than adrafinil for inducing wakefulness. It is essentially insoluble in water (which poses problems with respect to administration and bioavailability in experimental animals).

When modafinil is given orally in a single dose, absorption is slow;  $T_{max}$  is between two and four hours. The consumption of food with modafinil does not modify its pharmacokinetic profile. Modafinil metabolizes to modafinil acid, modafinil sulfone and hydroxy modafinil. Only the acid and sulfonic metabolites have been found in the plasma and urine of human subjects. Both of these metabolites are pharmacologically inactive. Urinary

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elimination of unconverted modafinil is low (approximately 10% of the administered dose). The elimination half-life of modafinil is somewhere between ten and thirteen hours. When multiple doses are given orally (200 mg/d), steady state plasma concentration is achieved within two to four days. Enzyme induction is not triggered at this dose level.

Modafinil has a low level of toxicity; its LD<sub>50</sub> is higher than 1 g/kg in rodents (when administered orally) and approximately 400 mg/kg in canines. Acute and chronic toxicity levels are also low with modafinil: when it is administered for 25 weeks to rats in doses of 20 and 50 mg/kg/d, no toxic effects are observed. Similarly, *in vitro* and *in vivo* mutagenesis tests reveal no anomalies and life-long carcinogenicity studies conducted in experimental animals (rats and mice) have produced no suspicious signs of cancer.

## PHARMACOLOGICAL INTEREST FOR HEALTHY SUBJECTS

Experiments involving healthy human subjects are comparatively rare. The data which is currently available concerns control group subjects who have participated in hypersomnia studies. In one such study, conducted by Benoit et al.,<sup>1</sup> a 200-mg dose of modafinil administered at 10 p.m. to a group of twelve young men was shown to reduce nocturnal sleepiness, (although the level of vigilance attained was less than the reference level), and to improve nocturnal psychomotor performance. In 1987, Goldenberg et al.<sup>2</sup> demonstrated that a group of twelve healthy subjects (five men and seven women) who had been given modafinil (200 mg three hours after breakfast) had multiple sleep latency test (MSLT), quantified EEG and analogue-visual-chart results that were not significantly different from those of the control group.

Much of the data currently available was produced in experiments involving subjects who had been deprived of sleep for periods of varying duration. The first of these experiments was conducted by Puech and Bensimon<sup>3</sup> with twelve healthy subjects who had been deprived of sleep for 36 hours. The investigators found that modafinil (at doses of 100, 200 and 300 mg/kg) antagonized the effects of sleep deprivation in a dose-dependent fashion. Lagarde et al. (1990 and 1992, published at a later date) have demonstrated the potent wakening effect obtained with modafinil when a 200-mg dose is administered for three consecutive days (Fig. 2), as well as the

potentiation of the recuperative effect of short naps when the drug is taken during the day. The similarity of EEG results in subjects given modafinil and those given a placebo was confirmed by Saletu et al.,<sup>7</sup> as was the absence of side-effects when modafinil was administered in doses of 100 and 200 mg.<sup>7,8</sup> In 1994, Bourdon et al.<sup>9</sup> demonstrated that modafinil had no effect on heat production under neutral conditions, nor on body temperature regulation in subjects exposed to cold. More recently (1995), Pigeau et al.<sup>10</sup> and Buguet et al.<sup>11</sup> compared modafinil and d-amphetamine and showed, among other things, that the two substances were almost equally effective at stabilizing mood and maintaining performance.

The assessment of modafinil in healthy subjects offers a way to demonstrate the potent wakening effect of this molecule which permits the maintenance of optimum capacity, produces no side-effects at effective dose levels, and has the original property of inducing wakefulness without interfering with sleep.

## MECHANISM OF ACTION

Hyperlocomotor activity, behavioural indices of arousal, and EEG results obtained after the administration of modafinil, have been examined in attempting to elucidate the mechanism of action which induces the wakening effect of this molecule.

### Pathways of Waking

There are four main subcortical systems which can trigger waking at the level of the cerebral cortex (Fig. 3):

- a direct ponto-cortical pathway, issuing from the noradrenergic neurons of the locus coeruleus or the serotonergic nuclei of the dorsal raphe;
- a ponto-basalo-cortical and ponto-hypothalamo-basalo-cortical pathway, issuing from the non-cholinergic neurons of the dorsolateral pontine tegmentum and the neurons of the posterior hypothalamus, (these neurons perform a relay function via the nuclei of the telencephalon), and ending in the cerebral cortex;
- a ponto or bulbo-hypothalamo-cortical pathway, issuing from cholinergic or non-cholinergic neurons in the magnocellular nucleus or dorsolateral pontine tegmentum, in which these neurons perform a relay function via the histaminergic neurons of the posterior hypothalamus which project to the cerebral cortex;

- a reticulo-thalamo-cortical pathway, issuing from the cholinergic neurons of the mesencephalic reticular formation which stimulate cerebral cortex activity through the intervention of the excitatory amino acid neurons (glutamate and/or aspartate) of the intermediate nucleus of the thalamus.

In short, these “waking neurons” call on many different neurotransmitters and share an essential anatomical characteristic; some of their extensions directly reach the cerebral cortex, while others connect with structures which in turn project to the cortex. Through these extensions, the cortex receives the transmitters which activate the “waking neurons.” The neurochemistry of waking states is as complex as the neuronal circuitry on which it depends. Since knowledge in this area is developing at a rapid pace, one must be prudent about proposing simplified (and therefore inaccurate) configurations of the systems which govern the sleep-waking cycle.

Modafinil’s chief pharmacological property is that it induces wakefulness, as opposed to stimulation, which has only occurred in mice and monkeys that were given high doses.<sup>12,13</sup> This distinguishes modafinil from psychostimulant amphetamines (the reference substances), which have different mechanisms of action and side-effects. In modafinil, the mechanism of action is particularly complex and enlists most of the transmitters involved in the neurochemical pathways of waking.

### Adrenergic System

Central  $\alpha$ 1-adrenergic receptor antagonists (prazosin and phenoxybenzamine) diminish the electroencephalographic and behavioral waking effects of modafinil in monkeys<sup>14</sup> and cats.<sup>15</sup> Alpha 2-adrenergic antagonists (yohimbine) and beta-adrenergic antagonists have no effect. Alpha-methyl-para-tyrosine, an inhibitor of catecholamine synthesis, has essentially no effect on modafinil-induced hyperactivity. In the context of the adrenergic system, modafinil appears to act as an  $\alpha$ 1-postsynaptic receptor agonist and does not require the participation of newly synthesized catecholamines. On the contrary, once monoamine reserves have been depleted by reserpine,<sup>12</sup> modafinil-induced hyperlocomotor activity is antagonized. It would seem that the mechanism of action of modafinil requires the participation of monoamine reserves. In addition, the effects of modafinil are not potentiated by noradrenalin re-

uptake inhibitors (desipramine or maprotiline), nor by monoamine oxidase inhibitors (MAO inhibitors) such as nialamide and pargyline. Consequently the presence of “physiological” central  $\alpha$ 1-adrenergic tone is indispensable to the manifestation of the stimulant or wakening effects of modafinil.

### Dopaminergic System

When modafinil is administered in low doses, its mechanism of action does not appear to require activation of the central dopaminergic systems.<sup>16</sup> In the rat, doses of up to 512 mg/kg given orally do not induce stereotypic or rotatory behaviors. In the dopamine-rich cerebral structures which regulate waking, such as the caudate nucleus, the striatum and the nucleus accumbens, modafinil (in doses of 16, 64 and 256 mg/kg) does not alter the maximum amplitude of catechol oxidation peaks. A dose of 30 mg/kg i.p. does not alter the concentrations of dopamine and its metabolites DOPAC and HVA in the dorsal striatum of the anesthetized rat.<sup>17</sup> At a concentration of  $10^{-5}$  M, modafinil does not increase the spontaneous release of [<sup>3</sup>H]-dopamine in mouse striatal synaptosomes. The dopaminergic system inhibitors haloperidol (0.125 mg/kg), pimozide (0.125 mg/kg) and sulpiride (32 mg/kg) do not modify modafinil-induced hyperactivity in rodents.<sup>16</sup>

However, behavioral and electroencephalographic studies conducted with Rhesus monkeys have demonstrated that pimozide (0.02 mg/kg) partially antagonizes the wakening effects of modafinil administered at doses of 12 to 45 mg/kg.<sup>14</sup>

Recent *in vivo* microdialysis studies in the anesthetized rat<sup>18</sup> show that modafinil (in doses above 100 mg/kg, s.c.) produces an increase in dopamine concentration in the posteromedial nucleus accumbens. Dopamine release occurs as a consequence of reduced GABAergic transmission, with the involvement of the serotonergic terminals. In addition, Gold and Balster<sup>19</sup> demonstrated in 1996 that the administration of high doses of modafinil in the rat (250 mg/kg, i.p.) reinforced addictive behavior to cocaine (although at a rate 200 times lower than with amphetamine or ephedrine). An indirect increase in dopaminergic transmission, resulting from the cessation of GABAergic inhibition and/or the blocking of dopamine re-uptake, may contribute to the effects produced by modafinil at high dose levels.<sup>18,19</sup>

## Serotonergic System

In the guinea-pig, chronic administration of modafinil (30 mg/kg/day for seven days, s.c.) does not alter concentrations of serotonin in the parietal cortex and neostriatum.<sup>20</sup> In the mouse (30 mg/day for fourteen days, i.p.) and the rat (50 mg/kg, i.p.) modafinil does not alter serotonin concentrations but does cause an increase in the serotonin metabolite 5-HIAA, as well as an increase in the speed at which it renews itself in the striatum. In the guinea-pig, the repeated administration of modafinil (30 mg/kg/day, for seven days, s.c.) counteracts the decrease in parietal cortex serotonin concentration induced by the intracerebroventricular administration of 5,7 DHT (a toxin to serotonergic neurons). In addition, administration of this serotonergic antagonist causes a moderate increase in noradrenalin in the parietal cortex. This increase is potentiated by modafinil.<sup>20</sup>

Consequently, it appears that serotonergic transmission is also implicated in the mechanism of action of modafinil.

## Histaminergic and Cholinergic Systems

*In vitro*, modafinil does not modify the release of histamine (whether spontaneous or induced by depolarization) and does not counteract the inhibitor effects which histamine has on its own release. Modafinil acts as neither an agonist nor an antagonist to H3 histaminergic receptors. (H3 presynaptic receptor antagonists induce waking.)

In the guinea-pig, modafinil (3-30 mg/kg, s.c.) does not modify the outflow of cortical acetylcholine.<sup>20</sup>

Consequently, it seems unlikely that the histaminergic and cholinergic systems are implicated in modafinil's mechanism of action.

## GABAergic and Cyclinergic Systems

Modafinil (3-30 mg/kg, s.c.) inhibits cortical  $\gamma$ -aminobutyric acid (GABA) outflow in a dose-dependent fashion in the unrestrained rat.<sup>20</sup> This result was confirmed in the anesthetized rat.<sup>21</sup> This inhibition of cortical GABA outflow is antagonized by the administration of methysergide (a 5-HT receptor antagonist) and ketanserin (a 5-HT<sub>2</sub> receptor antagonist). It is not modified by the (i.p.) administration of prazosin (an  $\alpha$ 1-adrenergic receptor antagonist). Consequently, the reduction in cortical GABA release may contribute to the

wakening action of modafinil. This modafinil-induced reduction in cortical GABA release does not occur when animals are pre-treated with 6-hydroxydopamine (a toxin to catecholaminergic neurons).<sup>16</sup> Therefore, the presence of catecholaminergic tone is essential. In fact, intracerebroventricular injection of modafinil increases GABA release in animals given 5,7 DHT (a specific neurotoxin to 5-HT neurons). The enhanced release of cortical GABA which modafinil induces in animals that have been pre-treated with 5,7 DHT is antagonized by prazosin.

These experiments show that modafinil-induced regulation of cortical GABA is linked to the balance between central serotonergic and  $\alpha$ 1-adrenergic transmissions.

In addition, reduced outflow of cortical glycine has been demonstrated by microdialysis.<sup>21</sup> This inhibitory transmitter amino acid is often found in the same nerve endings as GABA.

## Excitatory Amino Acids (EAA)

It is now recognized that excitatory amino acids (EAA) and their receptors participate in the systems that regulate waking.<sup>22</sup> It is also likely that EAA are implicated in the waking and neuroprotective properties of modafinil. A proton study using two-dimensional NMR spectroscopy<sup>23</sup> in the rat has shown that modafinil (600 mg/kg, i.p.) increases the level of aspartate ( $72 \pm 15\%$ ) and the glutamate-glutamine pool ( $28 \pm 8\%$ ) in the cortex. A complementary microdialysis study<sup>21</sup> has demonstrated the occurrence of a moderate transitory increase, followed by a prolonged decrease, in the level of extracellular glutamate in the rat brain cortex. Modafinil also induces a prolonged and significant decrease in the level of extracellular aspartate. Finally, an actographic behavioral study conducted in mice<sup>24</sup> has shown that the increase in motor activity induced by modafinil (100 mg/kg) can be modulated by various glutamate agonists and antagonists. This would suggest that modafinil acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, a non-NMDA receptor agonist, and a metabotropic receptor agonist. However, the EAA-release inhibitor propentofylline has not been shown to antagonize modafinil-induced hyperlocomotion. Consequently, it would appear that the early release of glutamate observed in microdialysis is not the direct cause of modafinil-induced motor stimulation.

## Metabolic and Energetic Effects

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Two-dimensional NMR spectroscopy<sup>23</sup> of the rat brain cortex has shown that modafinil (600 mg/kg, i.p.) triggers an increase in the creatine-phosphocreatine pool. This phenomenon may play a role in the energy-dependent re-uptake mechanisms which are engaged following the massive release of EAA and, accordingly, may contribute to the neuroprotective effect of modafinil in physiopathological situations such as hypoxia or exposure to neurotoxic organophosphate agents.

In a complementary study using phosphorus-31 NMR, cerebral phosphomonoesters increased and cerebral phosphodiester decreased following the administration of modafinil.<sup>22</sup> This may reflect the effects of modafinil on membranous phospholipids.<sup>25</sup>

Microdialysis following the administration of modafinil also showed a decrease in extracellular glutamine and alanine.<sup>21</sup> A decrease in the extracellular presence of these amino acids (which play a strictly metabolic role) may also contribute to the production of cerebral energy through the tricarboxylic cycle.

### Site of Action

Determining the site of action of modafinil through the traditional method, which involves the displacement of receptor-labelled ligands, was not possible.<sup>16</sup> Every *in vitro* attempt produced a negative result, with the exception of dopamine-carrier binding sites in the striatum of the guinea pig and the rat, where modafinil displaced labelled ligands (<sup>3</sup>H]-WIN35,428 or [<sup>3</sup>H]-mazindol).<sup>26</sup>

This led the team of professor Jouvet in Lyon<sup>27</sup> to investigate the proto-oncogene *c-fos*, a non-specific neuron activation marker. The Jouvet team observed that modafinil (1-5 mg/kg, p.o.) induces *c-fos* expression in the cat, where this largely occurs in the anterior hypothalamic nucleus. The vigilance-enhancing substances of reference, amphetamine and methylphenidate, do not induce *c-fos* expression in this structure but rather in the striatum and the whole cortex, which are dopamine targets. These results suggest that the anterior hypothalamic nucleus is the specific, privileged site of action of modafinil, inducing wakefulness through mechanisms which are distinct from those of traditional wakefulness-inducing substances.

In summary, although it is difficult to establish a hierarchy of the various neurochemical effects induced by modafinil, postsynaptic  $\alpha$ 1-adrenergic effects appear to be preponderant. At high dose levels, dopaminergic effects are induced and the transmitter amino acid system is brought into play. In addition, the effects of modafinil on energy metabolism within the cerebrum should not be overlooked.

## NEUROPROTECTION

Modafinil has a protective effect against hyperoxic convulsions induced in the mouse.<sup>28</sup> More recent experiments with Rhesus monkeys<sup>29</sup> have strengthened arguments in support of the potential neuroprotective properties of modafinil. One month prior to the experiments, sixteen superficial electrodes were implanted in the animals in order to record electrical activity in the cortex (electrocorticogram). In addition, two electromyogram electrodes were implanted in the muscles at the back of the neck. Hypoxia lasting 60 minutes, corresponding to an artificial altitude of 5,500 meters (72% SaO<sub>2</sub>), was induced in a hyperbaric chamber. Behavioral observation, as well as an analysis of electrical activity in the cortex of the Rhesus monkey in a state of hypoxia, demonstrated that modafinil (6 and 12 mg/kg) reduced sleepiness and increased vigilance. This led the investigators to hypothesize that the neuroprotective effects of modafinil may result from the modulation of several neurotransmission systems, in particular those which bring into play excitatory amino acids (EAA) and their NMDA receptors.

Neurotoxic organophosphate agents such as soman (potential tools of chemical warfare), target acetylcholinesterase (AChE) and cause the accumulation of acetylcholine (ACh). The acute administration of soman in laboratory animals brings about generalized convulsive seizures, as well as neuropathological sequelae in the subjects that survive. This occurs in all limbic areas, the hippocampus in particular. The occurrence of seizures is dependent on muscarinic cholinergic mechanisms. Recent studies<sup>30</sup> have shown that the massive release of excitatory amino acids (particularly glutamate) which follows soman poisoning likely plays a preponderant role in the propagation and maintenance of seizures, as well as in the delayed neuronal damage that occurs as a result of the activation of NMDA receptors. Consequently, soman poisoning appeared to provide an excellent neurotoxicity model to objectively

test the neuroprotective properties of modafinil. Omega-3 sites are peripheral benzodiazepine receptors largely present in glial cells and macrophages, and mostly absent in neurons. The increased density of omega-3 sites is a reflection of glial reaction and macrophagic colonization, which are consequences of acute or chronic neuronal distress. Consequently, the density of omega-3 sites provides an indirect index of cerebral lesions. An initial series of experiments conducted in the mouse (Fig. 4) demonstrated that modafinil, administered at doses of 600 mg/kg, i.p., antagonized density increases in omega-3 sites in the hippocampus following soman poisoning ( $DL_{50}=220$ ). However, modafinil doses of 150 and 300 mg/kg, i.p. did not antagonize density increases in omega-3 sites. A second series of experiments consisted of the microscopic examination (with cresyl violet coloration) of hippocampal sections in soman-poisoned rats, where some of the rats had been pretreated with modafinil and some had not. In view of the results previously obtained in the mouse, the test was conducted using only a dose of 600 mg/kg i.p. The hippocampus of the poisoned rats that had not been pretreated showed microscopic lesions or ruptures in the pyramidal cell layer as well as signs of cytolysis. In rats pretreated with modafinil, the CA1 and CA3 areas showed no visible microscopic lesions and the pyramidal cell layer had maintained its integrity. Hippocampal histologic sections in rats pretreated with modafinil were not visibly different from those of non-poisoned rats. These two studies, conducted at the Centre de Recherches du Service de Santé des Armées,<sup>31</sup> clearly show that, at a dose level of 600 mg/kg, modafinil plays a neuroprotective role, preventing hippocampal lesions induced by neurotoxic organophosphate agents.

The neuroprotective properties of modafinil may be linked to the prolonged decrease in extracellular EAA which it induces, as well as to its properties as an NMDA receptor antagonist and metabotropic receptor agonist.

These preliminary results, which provide an understanding of the neuroprotective mechanisms of modafinil, may have therapeutic applications, particularly in the context of exposure to neurotoxic organophosphate agents.

## CONCLUSION

Because of its wakening effect, which is not associated with undesirable side effects, its recently

discovered neuroprotective properties and its original mechanism of action, modafinil is a highly interesting molecule from the standpoint of military use. A number of aspects relating to the potential use of modafinil in an operational setting still have not been closely examined. Both the Centre de Recherche du Service de Santé des Armées and the Instituts are actively pursuing such investigations in order to ensure that combatants can conduct their missions safely and effectively.

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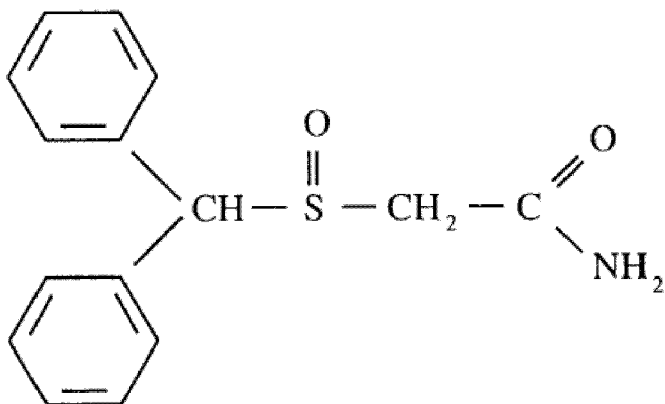
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**Figure 1: Modafinil Molecule**



Molecular formula: C<sub>15</sub> H<sub>15</sub> NO<sub>2</sub> S

Relative molecular mass: 273.36

Chemical identity: 2-[(diphenylmethyl)sulfinyl] acetamide

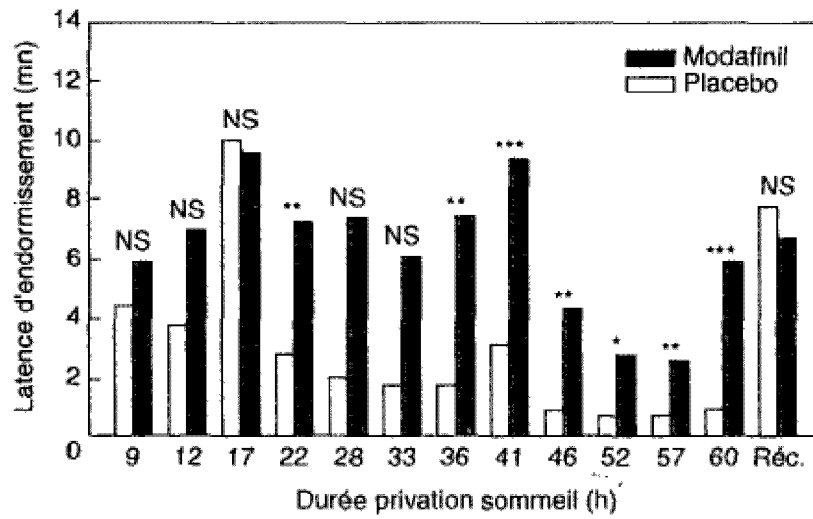
Commercial name: Modiodal®, Laboratoire L. LAFON

Characteristics:

White crystalline powder: practically insoluble in water, sparingly soluble in ethanol, soluble in methanol.

Modafinil melts at 150-155 degrees centigrade with thermal decomposition.

**Figure 2: Mean Sleep Latencies in a 60-Hour Sleep Deprivation Experiment**



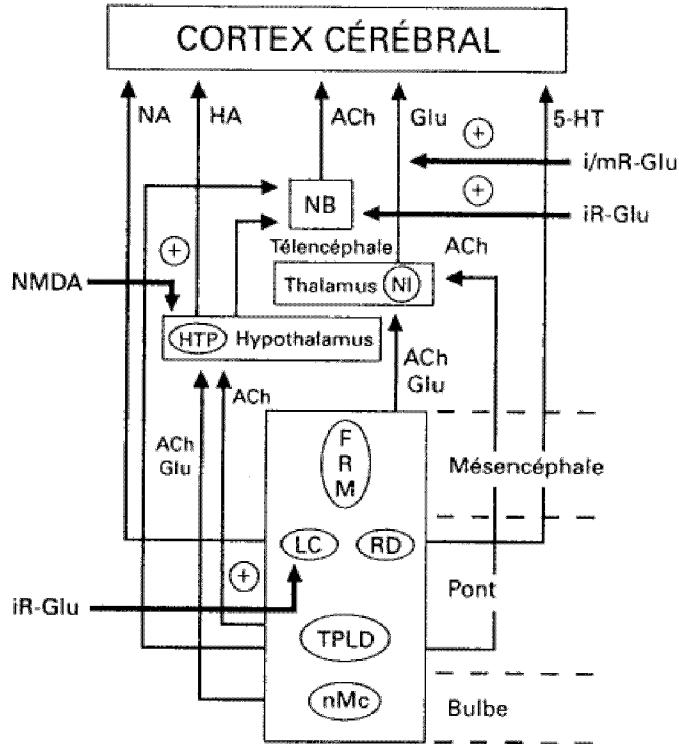
Vertical scale: Sleep latency period in minutes (0 to 14)

Horizontal scale: Period of sleep deprivation in hours – 0 to 60 hours

Multiple Sleep Latency Test (MSLT) with placebo and modafinil (200 mg/8 hrs). NS = not significant.

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

**Figure 3: Schematic Representation of the Neurochemical Pathways of Waking**



ACh: acetylcholine

Glu: glutamate and/or aspartate

HA: histamine

5HT: serotonin

NA: noradrenalin

iR-Glu: ionotropic

glutamate receptors (NMDA and non-NMDA)

mR-Glu: metabotropic glutamate receptors

NMDA: NMDA receptors

MRF: mesencephalic reticular formation

BN: basal nucleus

IN: intermediate nucleus

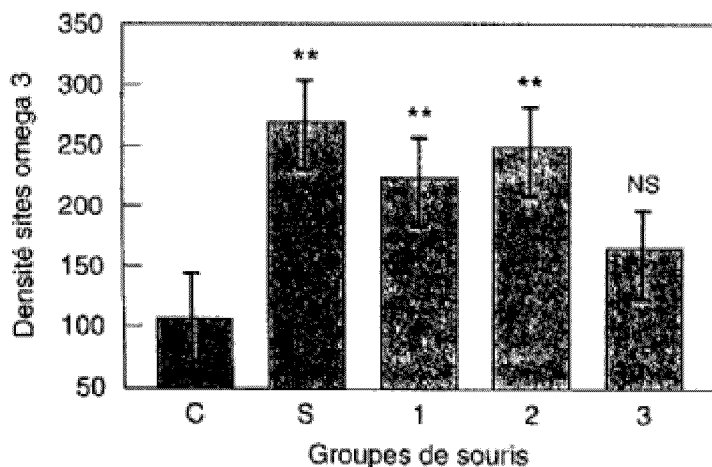
LC: locus coeruleus

MCn: magnocellular nucleus

DR: dorsal raphe

DLPT: dorsolateral pontine tegmentum

**Figure 4: Neuroprotective Effect of Modafinil.**



Densité des sites  $\omega_3$ , dans l'hippocampe de souris, 48 heures après intoxication par le soman (moyennes  $\pm$  e.s.m. exprimées en fmol/mg de protéine).

Groupes de souris : C = contrôle ; S = soman ; 1 = soman + modafinil (150 mg/kg) ; 2 = soman + modafinil (300 mg/kg) ; 3 = soman + modafinil (600 mg/kg).

Significativités exprimées par rapport au groupe contrôle :

\*\*  $p < 0,01$  ; NS : non significatif (Test de Mann et Whitney).

Vertical scale: Omega-3 site density (50 to 350)

Horizontal scale: Mouse groups (C – S – 1 – 2 – 3)

Omega-3 site density in the mouse hippocampus, 48 hours after soman poisoning (mean  $\pm$  S.E.M. expressed as fmol/mg of protein)

Mouse groups: C = control; S = soman; 1 = soman + modafinil (150 mg/kg); 2 = soman + modafinil (300 mg/kg); 3 = soman + modafinil (600 mg/kg).

Significance expressed in relation to the control group:

\*\*  $p < 0.01$ ; NS: insignificant (Mann and Whitney test).