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Central α_1-adrenergic stimulation in relation to the behaviour stimulating effect of modafinil; studies with experimental animals

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Single administration of the new drug modafinil was followed by an increase in locomotor activity in mice and in nocturnal activity in monkeys. Stereotyped behaviour in mice and rats, and potentiation of amphetamine-induced stereotyped behaviour were not observed; however, at the highest dose used, a slight potentiation of apomorphine-induced stereotyped behaviour was observed in rats. The modafinil-induced increase in locomotor activity in mice was prevented by the centrally acting α_1-adrenoceptor antagonists, prazosin and phenoxybenzamine, and by reserpine but not by the mixed dopamine D-1/D-2 antagonist, haloperidol, the dopamine D-2 antagonist, sulpiride, the peripherally acting α_1-adrenoceptor antagonist, phentolamine, the α_2-adrenoceptor antagonist, yohimbine, the β-adrenoceptor antagonist, propranolol, or by the catecholamine synthesis inhibitor, α-methyl-p-tyrosine. Likewise, the modafinil-induced increase in nocturnal activity in monkeys was prevented by prazosin. Interestingly, modafinil did not produce obvious peripheral sympathetic effects in mice and rats (no salivation, no contraction of the pilomotor muscles, slight mydriasis only at high doses). Therefore, modafinil appears to produce a strong stimulating effect in rodents and in primates. These effects could be linked to modulation (stimulation) of central α_1-adrenoceptors unaccompanied by peripheral sympathetic effects, which is unexpected.

Modafinil; Prazosin; α_1-Adrenoceptors; (Awakening); (Mouse); (Rat); (Monkey)

1. Introduction

Many psychotropic drugs, including amphetamine and non-amphetamine stimulants such as methylphenidate or amfonelic acid (Aceto et al., 1967), non-imipramine-like antidepressants such as nomifensine (Hoffmann, 1973), amineptine (Samanin et al., 1977) or bupropion (Soroko et al., 1977), and miscellaneous drugs like oxolinic acid, an urinary antiseptic (Chermat et al., 1979), increase locomotor activity in animals. Locomotor stimulation is usually followed by stereotyped behaviour, generally at higher doses, with catecholamine releasing drugs like amphetamine, or dopamine uptake inhibitors like methylphenidate (Costall and Naylor, 1974) and nomifensine (Hunt et al., 1974). An increased state of arousal has been reported in humans after most of these drugs, e.g. nomifensine (Nicholson et al., 1986), oxolinic acid (Galland et al., 1978).

In a previous study in which we searched for an agent which would be active in animal models used to predict the stimulating properties of drugs, but which differed chemically and pharmacologically from amphetamine- or methylphenidate-like drugs and which was without overt sympathomimetic effects, we found adrafinil, which demon-

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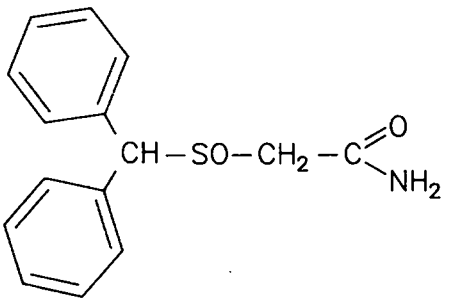

Fig. 1. Structural formula of modafinil (DCI): (diphenylmethyl)sulfinyl-2 acetamide.

strated a unique behavioural profile in mice (Duteil et al., 1979; Rambert et al., 1986) and monkeys (Milhaud and Klein, 1985). This drug increased locomotion or wakefulness without exerting peripheral sympathomimetic actions. As this molecule was partly metabolized to the amide form, modafinil (diphenylmethyl) sulfinyl-2 acetamide (fig. 1), it seemed worthwhile to synthesize this metabolite and to study its effects on locomotion, nocturnal activity and stereotyped behaviour in animals.

2. Materials and methods

2.1. Animals

Male NMRI mice (CERJ, Le Genest, France) weighing 18-25 g, male CD1 Sprague-Dawley rats (Charles River, Saint-Aubin-lès-Elbeuf, France) weighing 180-250 g, and male rhesus monkeys (Macaca mulatta, Charles River) weighing 3.7-5.6 kg were used. Mice and rats were housed in makrolon cages, in groups of 10 per cage, at a room temperature of about 21 ± 1°C and had free access to a standard diet (Extra-Labo). The animals were kept under an artificial light-dark cycle (light period from 6 h 30 a.m. to 6 h 30 p.m.). Home cages were brought from the animal quarters to the testing laboratory 16 h before testing to control transport stress and to allow habituation to test room conditions.

Monkeys were housed either in groups of 6-8 in a large cage (2 × 2 × 2 m) or in pairs in a stainless steel cage (0.5 × 0.6 × 0.7 m) in an environmentally controlled room with regulated temperature (21 ± 1°C) under a constant 12 h light/12 h dark cycle (light period from 6 a.m. to 6 p.m.). The monkeys were fed 3 times a day on a diet consisting of standard monkey pellets (Extra-Labo) supplemented with fresh fruit and vegetables, and had continuous access to water.

2.2. Experimental procedure

Animals were assigned to treatment groups using appropriate randomization procedures: randomized complete block design or latin-square design (Lellouch and Lazar, 1974). Drugs were administered by the intraperitoneal, oral or subcutaneous route in a volume of 20 ml per kg body weight in mice, 5 ml per kg body weight in rats and 10 ml per animal in monkeys. The doses of compounds refer to the salts. The control animals received the same number of injections of an appropriate volume of deionized water at the corresponding time intervals.

2.2.1. Mice and rats

Diurnal experiments were carried out between 8 a.m. and 5 p.m. at an ambient temperature of 21 ± 1°C in a noiseless, diffusely illuminated room. Behavioural effects were assessed by trained observers, who were uninformed as to the treatments given. Groups of 3 mice or rats were observed for 3 h to detect modafinil-induced gross behavioural changes and peripheral effects using a modification of the method described by Irwin (1962). Locomotor activity (number of crossed photocell beams) was recorded for 30 min after a single mouse was placed in a photocell actimeter (Dews, 1953; Boissier and Simon, 1965). Stereotyped behaviour was scored individually (on a 0 to 3 scale based on a 30-s observation, every 30 min for 2 h in mice and every 10 min up to the disappearance of the stereotypies in rats) after i.p. injected modafinil or amphetamine, or s.c. injected apomorphine. The stereotyped behaviour (compulsive sniffing, licking, biting, chewing, grooming or head-weaving) was scored as follows (Simon and Chermat, 1972): 0 = no stereotypies,

1 = scarce, low intensity stereotypies, 2 = frequent, intensive stereotypies, 3 = continuous, strong stereotypies. For each animal, the total stereotypy index represented the sum of the individual scores at each observation time.

2.2.2. Monkeys

Nocturnal activity was investigated in 4 pairs of monkeys according to a latin-square design: at 5 p.m., 2 animals of the same pair were given modafinil or vehicle by the oral route and were then placed in individual cages in the same soundproof room. The total mobility time was recorded individually for 12 h (from 6 p.m. to 6 a.m.) by an ultrasound device, and gross behaviour was assessed continuously by simultaneous videotape recording. For prazosin interaction testing, the same methodology was used for 4 pairs of monkeys orally treated with prazosin (2 $mg \cdot kg^{-1}$) at 4 p.m., 1 h before modafinil administration.

2.3. Drugs

Apomorphine HCl and d-amphetamine sulfate (Coopération Pharmaceutique Française), haloperidol (Haldol, Janssen-Le Brun), prazosin HCl (Pfizer), phentolamine methanesulfonate (Ciba) and dl-propranolol HCl (ICI) were dissolved in deionized water. α-Methyl-p-tyrosine, AMPT (Sigma), modafinil (Lafon), phenoxybenzamine HCl (SK&F) and sulpiride (Delagrange) were suspended in a 0.005% tragacanth gum solution. Reserpine (Coopération Pharmaceutique Française) was dissolved in glacial acetic acid (0.1 ml) and diluted to 100 ml in deionized water.

2.4. Statistics

Drug effects were assessed by either a one factor analysis of variance or a multifactor analysis of variance followed by a Newman-Keuls multiple-range-test or a two-tailed Dunnett's test in order to compare drug-treated groups with the appropriate control groups. A P value of 0.05 was accepted as the level of statistical significance (Schwartz, 1981).

3. Results

3.1. Overall observation

3.1.1. Mice

Hyperactivity and hyper-reactivity without stereotyped behaviour occurred for 2-3 h after i.p. modafinil in doses ranging from 4 to 256 $mg \cdot kg^{-1}$. A slight, short-lasting mydriasis was present for 30 min, but only after the highest dose used (256 $mg \cdot kg^{-1}$). Hyper-salivation and pilomotor muscle contraction were never observed.

3.1.2. Rats

At the lowest doses used (2 and 8 $mg \cdot kg^{-1}$ i.p.), modafinil did not produce any noteworthy behavioural or peripheral change. At higher doses (32 and 128 $mg \cdot kg^{-1}$ i.p.), hyperactivity and hyper-reactivity occurred, lasting 30 min to 2 h according to the dose, but stereotyped behaviour was never observed. Hyper-salivation or pilomotor muscle contraction did not appear but mydriasis occurred for 2 h, but only after high doses.

3.2. Effect on motor activity

3.2.1. Locomotor activity in mice

When administered 30 min before testing, modafinil (32-128 $mg \cdot kg^{-1}$ i.p. or p.o.) induced a strong dose-dependent increase in locomotor activity in mice. The modafinil-induced increase in locomotor activity was maximal 15 min after i.p. and 30-60 min after oral drug administration, and lasted from 1 h up to 4 h depending on the dose administered (fig. 2).

The hyperlocomotor activity induced by modafinil injected i.p. immediately before recording was prevented by the centrally acting α_1-adrenoceptor antagonists, prazosin (interaction $F(2,90) = 4.41$, $P = 0.015$) and phenoxybenzamine (interaction $F(2,138) = 10.98$, $P < 0.001$), but not by phentolamine (interaction $F(2,186) = 0.37$, $P > 0.05$) given 1 h before modafinil (table 1). Under the same conditions, the β-adrenoceptor antagonist, propranolol (interaction $F(2,90) = 0.77$, $P > 0.05$), and the dopamine D-2 receptor antagonist, sulpiride (interaction $F(2,138) = 0.38$, $P > 0.05$), did not significantly prevent modafinil-induced

hyperlocomotor activity whereas the preferential α_2-adrenoceptor antagonist, yohimbine, slightly potentiated the activity (interaction $F(2,186) = 3.59$, $P = 0.03$). The mixed dopamine D-1/D-2 receptor antagonist, haloperidol, which is also a potent α_1-adrenoceptor antagonist, strongly depressed spontaneous locomotor activity and reduced modafinil-induced locomotor activity by the same amount (interaction $F(3,232) = 1.38$, $P > 0.05$).

When given 1 h before recording, prazosin (1 or 2 $mg \cdot kg^{-1}$) decreased spontaneous locomotor activity. Prazosin (2 $mg \cdot kg^{-1}$) reduced modafinil (32-128 $mg \cdot kg^{-1}$)-induced hyperlocomotor activity. At 1 $mg \cdot kg^{-1}$ prazosin did not modify the hyperlocomotion induced by the lower doses of modafinil (32-64 $mg \cdot kg^{-1}$) but prevented the hyperlocomotion induced by the higher doses (96-128 $mg \cdot kg^{-1}$) of modafinil given i.p. 30 min before recording (interaction $F(8,561) = 3.676$, $P = 0.003$, fig 3). Although there was a clear depression of locomotor activity, inhibition of catecholamine synthesis by AMPT did not counteract modafinil-induced hyperlocomotion in mice (interaction $F(18,740) = 0.305$, $P > 0.05$, fig. 3) while reserpine (which interfers with catecholamine and indolamine storage) produced a dramatic decrease in spontaneous locomotor activity and significantly prevented modafinil-induced hyperlocomotion (interaction $F(15,552) = 3.674$, $P < 0.001$, fig. 3). Under the same conditions, in spite of this decrease in spontaneous locomotor activity, reserpine was

TABLE 1

Effects of some catecholamine receptor antagonists on modafinil-induced locomotor activity in mice. Catecholamine receptor antagonists were injected 1 h before modafinil. Locomotor activity (number of crossed photocell beams) was recorded immediately after modafinil administration for a 30-min period. (a) Significantly different ($P \leq 0.05$, Newman-Keuls test) from the control group receiving vehicle 60 min and 0 min before recording. (b) Significantly different ($P \leq 0.05$, Newman-Keuls test) from the group receiving vehicle and modafinil 60 min and 0 min before recording, respectively.

Catecholamine receptor antagonists	$mg \cdot kg^{-1}$ i.p.	Without modafinil			Modafinil 128 $mg \cdot kg^{-1}$ i.p.		
		Mice number	Locomotor activity		Mice number	Locomotor activity	
			Mean ± S.E.M.	Var.%		Mean ± S.E.M.	Var.%
Prazosin (α_1)	0	24	332 ± 29.0		24	994 ± 112.7 (a)	
	1	12	231 ± 52.5	−30%	12	570 ± 118.4 (b)	−43%
	2	12	197 ± 33.0	−41%	12	334 ± 60.5 (b)	−66%
Phenoxybenzamine (α_1)	0	36	278 ± 21.0		36	744 ± 43.4 (a)	
	8	12	196 ± 16.8	−30%	12	603 ± 91.1 (a, b)	−19%
	16	24	171 ± 21.2	−38%	24	264 ± 34.7 (b)	−65%
Phentolamine (α_1)	0	48	288 ± 18.5		48	656 ± 45.5 (a)	
	8	24	221 ± 18.5	−23%	24	525 ± 36.4 (a, b)	−20%
	16	24	184 ± 20.4	−36%	24	496 ± 62.6 (a, b)	−24%
Yohimbine (α_2)	0	48	298 ± 14.6		48	737 ± 35.8 (a)	
	0.5	24	341 ± 23.4	+14%	24	929 ± 52.3 (a, b)	+26%
	2	24	305 ± 25.0	+2%	24	718 ± 46.5 (a)	−3%
Propranolol (β)	0	24	226 ± 24.2		24	745 ± 70.4 (a)	
	16	12	203 ± 38.4	−10%	12	749 ± 120.9 (a)	+1%
	32	12	158 ± 27.0	−30%	12	544 ± 81.9 (a)	−27%
Haloperidol (D-1/D-2)	0	60	286 ± 15.7		60	641 ± 34.5 (a)	
	0.125	12	251 ± 37.8	−12%	12	617 ± 98.2 (a)	−4%
	0.25	24	175 ± 33.6	−39%	24	417 ± 33.8 (b)	−35%
	0.5	24	141 ± 32.0	−51%	24	374 ± 43.6 (b)	−42%
Sulpiride (D-2)	0	36	236 ± 15.4		36	540 ± 42.6 (a)	
	32	12	284 ± 48.1	+20%	12	603 ± 63.1 (a)	+12%
	64	24	153 ± 18.1	−35%	24	529 ± 52.7 (a)	−2%

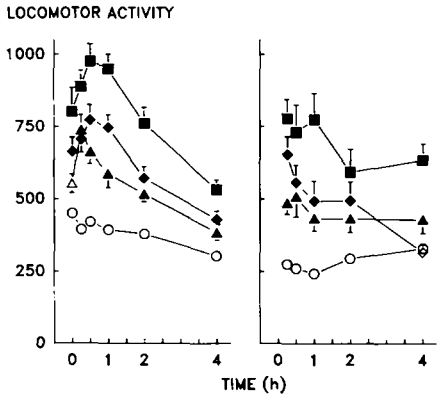

Fig. 2. Time course of locomotor activity after oral or intraperitoneal administration of modafinil in mice. Modafinil was administered by the oral (left panel) or intraperitoneal (right panel) route immediately (0 h, oral route only), 15 min, 30 min, 1 h, 2 h or 4 h before the mice ($n = 12$-24) were placed in a photocell activity meter device. Mean locomotor activity (number of crossed photocell beams recorded for a 30 min period) ± S.E.M. is shown. Vehicle = circles, modafinil 32 mg·kg^{-1} = triangles, modafinil 64 mg·kg^{-1} = diamonds, modafinil 128 mg·kg^{-1} = squares. Significant differences ($P \leq 0.05$) from appropriate control group (p.o. n = 60-72; i.p., n = 48) are represented in filled symbols (Dunnett's test).

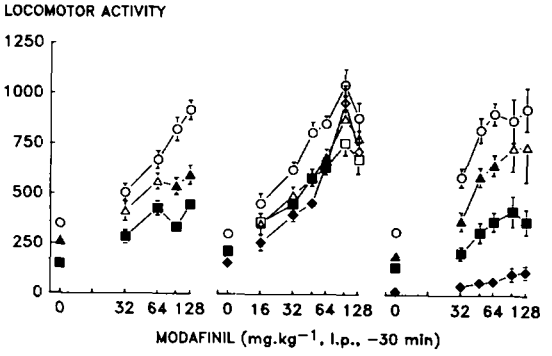

Fig. 3. Effects of prazosin, AMPT and reserpine on modafinil-induced locomotor activity in mice. Prazosin (left panel, n = 24-48), AMPT (middle panel, n = 12-48) and reserpine (right panel, n = 12-36) were administered 30 min, 3 h and 3 h 30 before modafinil, respectively. Mean locomotor activity (number of crossed photocell beams recorded 30 min after modafinil administration for a 30 min period) ± S.E.M. is shown. Left panel: vehicle = circles, prazosin 1 mg·kg^{-1} = triangles, prazosin 2 mg·kg^{-1} = squares. Middle panel: vehicle = circles, AMPT 50 mg·kg^{-1} = triangles, AMPT 75 mg·kg^{-1} = squares, AMPT 100 mg·kg^{-1} = diamonds. Right panel: vehicle = circles, reserpine 0.25 mg·kg^{-1} = triangles, reserpine 0.5 mg·kg^{-1} = squares, reserpine 1 mg·kg^{-1} = diamonds. Significant differences ($P \leq 0.05$) from the group receiving vehicle at the appropriate time (1 h, 3 h 30 or 4 h before recording) and modafinil at the same dose level, 30 min before recording, are represented in filled symbols (Dunnett's test).

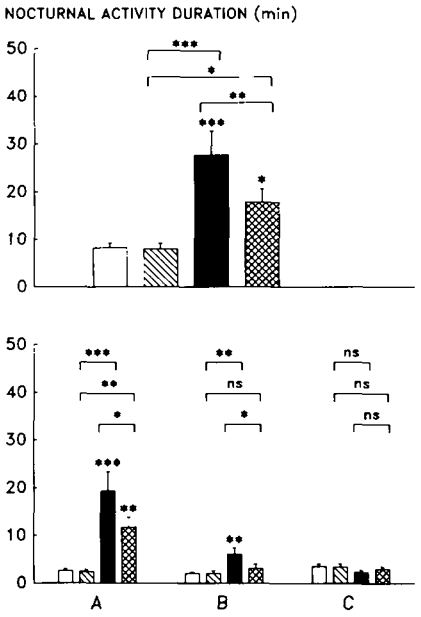

Fig. 4. Effects of prazosin on the modafinil-induced increase in nocturnal activity in monkeys. Prazosin (2 mg·kg^{-1}) was given orally 1 h before modafinil (32 mg·kg^{-1}) was given p.o. at 5 p.m. (8 animals/dose). The mean total nocturnal activity duration ± S.E.M. for the whole night, recorded from 6 p.m. to 6 a.m. (upper panel), and for each third of the night (lower panel, A: 6 p.m. to 10 p.m., B: 10 p.m. to 2 a.m., C: 2 a.m. to 6 a.m.) is shown. Vehicle-vehicle: open bar, prazosin-vehicle: hatched bar, vehicle-modafinil: filled bar, prazosin-modafinil: crossed bar. Significant differences between groups (Newman-Keuls test) are represented as ns: not significant ($P > 0.05$); * $0.01 < P \leq 0.05$; ** $0.001 < P \leq 0.01$; *** $P \leq 0.001$.

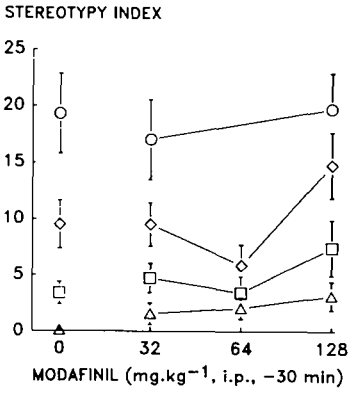

Fig. 5. Amphetamine-induced stereotyped behaviour in rats: effect of modafinil. Amphetamine (i.p.) was given 30 min after modafinil (i.p.) injection (6 or 12 rats/dose) Mean stereotypy index ± S.E.M. is shown. Amphetamine 0.25 mg·kg^{-1} = triangles, 0.5 mg·kg^{-1} = squares, 1 mg·kg^{-1} = diamonds, 2 mg·kg^{-1} = circles. Differences between groups receiving modafinil and amphetamine and groups receiving vehicle and amphetamine at the same dose level were not significant (Dunnett's test).

unable to prevent amphetamine (3-6 mg · kg $^{-1}$)-induced hyperlocomotor activity (data not shown).

3.2.2. Nocturnal activity in monkeys

Modafinil (16-64 mg · kg $^{-1}$, p.o.) increased the duration of nocturnal activity but statistical significance was only reached with the highest dose used (mean nocturnal activity duration ± S.E.M.: control, 8.69 ± 1.66; 16 mg · kg $^{-1}$, 14.60 ± 2.67, $P > 0.05$; 32 mg · kg $^{-1}$, 30.93 ± 8.92, $P > 0.05$; 64 mg · kg $^{-1}$, 85.17 ± 22.38, $P < 0.001$). This effect was more obvious during the first third of the night but was still present throughout the night after the highest dose. In a separate experiment, modafinil (32 mg · kg $^{-1}$ p.o.) induced a significant increase in duration of nocturnal activity, an effect which was significantly reduced by prazosin (2 mg · kg $^{-1}$, p.o.) given 1 h before modafinil (fig. 4).

3.3. Stereotyped behaviour

3.3.1 Mice

Modafinil, in doses up to 128 mg · kg $^{-1}$ i.p., did not produce significant stereotyped behaviour in mice. The stereotypy index was only slightly increased after a high dose of modafinil (256 mg · kg $^{-1}$) whereas d-amphetamine (4-8 mg · kg $^{-1}$ i.p.) induced strong, long-lasting stereotypies. Under the same conditions, apomorphine (4 mg · kg $^{-1}$ s.c.) produced a strong but short-lasting stereotyped behaviour.

3.3.2. Rats

In doses up to 256 mg · kg $^{-1}$ i.p., modafinil did not induce stereotyped behaviour in rats. Conversely, d-amphetamine (0.5-2 mg · kg $^{-1}$ i.p.) produced strong long-lasting, dose-dependent stereotypies, and apomorphine (0.5 mg · kg $^{-1}$ s.c.) produced a strong but short-lasting stereotyped behaviour. Modafinil, in doses from 2 to 32 mg · kg $^{-1}$ i.p., did not modify apomorphine (0.5 mg · kg $^{-1}$ s.c.)-induced stereotyped behaviour in rats, but the highest dose used (128 mg · kg $^{-1}$) slightly but significantly potentiated this behaviour (table 2). In doses up to 128 mg · kg $^{-1}$ i.p., modafinil did not significantly potentiate or prevent amphetamine (0.25, 0.5, 1 or 2 mg · kg $^{-1}$ i.p.)-induced stereotyped behaviour in rats (fig. 5).

TABLE 2

Effects of modafinil on apomorphine-induced stereotyped behaviour in rats. Apomorphine (0.5 mg · kg $^{-1}$ s.c.) was injected 30 min after administration of modafinil (6 rats/dose). (a) Significantly different ($P \leq 0.05$) from the control group (Dunnett's test).

Modafinil mg · kg $^{-1}$ i.p.	Total stereotypy index (mean ± S.E.M.)	Stereotypy duration (min) (mean ± S.E.M.)
0	13.0 ± 0.26	48 ± 1.7
2	13.0 ± 0.26	50 ± 0.0
8	12.7 ± 0.21	48 ± 1.7
32	13.0 ± 0.26	50 ± 0.0
128	14.8 ± 0.75 (a)	62 ± 4.0 (a)

4. Discussion

Locomotor activity was increased in mice after oral or intraperitoneal administration of modafinil over a large dose range. The apparent greater potency of modafinil when given by the p.o. compared to the i.p. route was probably related to higher basal locomotor activity of the control group given vehicle by the p.o. route compared to that of the control group given vehicle by the i.p. route. The magnitude and duration of this hyperlocomotion, which was rapid in onset, were dose-dependent. Likewise, an increase in nocturnal activity in monkeys was seen after oral modafinil. Thus, in spite of its poor solubility in water, modafinil was able to produce behavioural effects, which suggests that this compound is able to cross the intestinal and the blood-brain barriers.

It is well established that brain noradrenaline and dopamine are the two neurotransmitters mainly involved in the central control of locomotor activity (Andén et al., 1973). Noradrenaline given into the lateral ventricle of the brain of conscious mice increases locomotor activity and this effect is prevented by phenoxybenzamine but not by propranolol (Herman, 1975). Dopamine also increases locomotor activity under the same conditions, and, at higher doses, induces stereotyped behaviour; both these effects are blocked by

pimozide (Herman, 1975). Moreover, acute injection of dopamine into the nucleus accumbens of rat induces a neuroleptic-sensitive increase in spontaneous locomotor activity (Costall et al., 1984) which cannot be mimicked by other neurotransmitters infused into the nucleus accumbens. The relative importance of dopamine and noradrenaline in the control of drug-induced hyperactivities differs, however, according to the drug, the animal species and the experimental procedure. Both brain noradrenaline and dopamine (Handley and Thomas, 1978) appear to be necessary for the development of amphetamine-elicited stimulation in normal mice, while brain dopamine alone is claimed to be of major importance for the central stimulant action of dexamphetamine in rats (Hollister et al., 1974) and reserpinized mice (Svensson, 1970). On the other hand, 'non-amphetaminic' stimulants including methylphenidate (Thornburg and Moore, 1973) and amfonelic acid (Mc Millen and Shore, 1978) have been reported to act on dopamine neurons without affecting noradrenaline neurons in the rat.

Our results demonstrate a prominent role of noradrenaline in the modafinil-induced hyperlocomotor activity in mice and nocturnal awakening in monkeys. These effects were prevented by peripherally injected drugs in doses known to cause blockade of the central α_1-adrenoceptors: prazosin (Menkes et al., 1981) and phenoxybenzamine (Andén and Strömbom, 1974), but not phentolamine, which does not easily enter the brain (Andén and Strömbom, 1974). Prazosin and phenoxybenzamine have been reported to act preferentially at postsynaptic α_1-adrenoceptors (Hua and Moulds, 1978; Massingham et al., 1981). Intact central postsynaptic α_1-adrenoceptors seem therefore to be required for the development of modafinil-induced hyperactivity in mice and the stimulation of nocturnal activity in monkeys. These results are consistent with those of numerous studies demonstrating an increase in locomotor activity following administration of α_1-adrenoceptor agonists, which are usually injected centrally owing to their poor and slow penetration into the brain (Clineschmidt et al., 1980). Such an α_1-adrenoceptor-mediated behavioural change, including coordinated locomotor activity, was reported after intracerebroventricular injection of noradrenaline (Herman, 1975), phenylephrine and methoxamine in normal (Heal, 1984) or reserpinized mice (Holz et al., 1982) and after intracisternal injection in rats (Clineschmidt et al., 1979). These behavioural effects, which can be differentiated from the behavioural and locomotor effects of dopaminergic, 5-hydroxytryptaminergic or opiate drugs, were inhibited by prazosin or phenoxybenzamine but not by yohimbine or propranolol. However, we could not determine locomotor activity after central injections of modafinil because of the lack of water solubility of the drug.

An indirect involvement of endogenous noradrenaline stimulating α_1-adrenoceptors could account for the modafinil-induced hyperlocomotor activity in mice since this effect was abolished by reserpine, a drug known to deplete catecholamines (Carlsson et al., 1966; Bareggi et al., 1979). However, unlike amphetamine-induced hyperlocomotion (Svensson, 1970), modafinil-induced hyperlocomotion was not prevented by inhibition of tyrosine hydroxylase by AMPT. Thus the noradrenaline stores insensitive to AMPT (Glowinski et al., 1972; Thierry et al., 1973) appear to be of major importance in the modafinil-induced increase in locomotor activity in mice. In addition, the control of locomotor activity in rats has been related to activity in the locus coeruleus, with α_1- and α_2-adrenoceptors playing opposite roles (Velley et al., 1982); moreover, in mice, hyperactivity might result from activation of α_1-adrenoceptors whereas sedation results from activation of α_2-adrenoceptors (Pichler and Kobinger, 1981).

Noradrenaline-containing cells within the locus coeruleus (Dahlström and Fuxe, 1964) are more active during periods of waking and less active during REM sleep, leading to the hypothesis that the locus coeruleus noradrenergic system is involved in vigilance and arousal (Aston-Jones, 1985). Its projections to the cerebral cortex have been suggested to be involved in initiating or maintaining stages of the sleep-waking cycle (Fuxe et al., 1974) by activation of cortical α_1-adrenoceptors (De Sarro et al., 1987).

However, the lack of α_1-related peripheral sympathomimetic effects in our studies and in cardiovascular studies in rats and dogs (unpub-

lished data) remains unexplained at the moment. Modafinil could indirectly enhance α_1-adrenoceptor stimulation by mechanisms above or below the coeruleo-cortical noradrenergic pathways. It could also play a role in heterostatic mechanisms, by receptor-receptor interactions (Fuxe and Agnati, 1985), leading to a further increase in the number of possible messages across the membrane, or by allowing filtration of the signals reaching the post-synaptic membrane, leading to a more subtle modulation of transmission. An involvement of β-adrenoceptors in the control of the sleep-waking cycle cannot be ruled out completely (Monti, 1982), but these receptors can be excluded from involvement in the modafinil-induced locomotor activity in mice since this effect was not significantly prevented by the β-adrenoceptor antagonist, propranolol.

The involvement of a dopaminergic mechanism in the central effects of modafinil cannot be substantiated. The dopaminergic blocking drugs, sulpiride and haloperidol, did not prevent modafinil-induced hyperlocomotion in mice. In fact, in spite of a strong locomotor depression produced by haloperidol, the relative increase above basal activity was not significantly altered. Under these conditions, the expected antagonism of modafinil-induced hyperlocomotion related to the potential α_1-adrenoceptor blocking properties of haloperidol was not demonstrated: these α_1-adrenoceptor blocking properties are only obvious at doses higher than those needed to produce dopamine receptor blockade and major locomotor depression. Unlike the modafinil induced hyperlocomotor effects, amphetamine-induced hyperlocomotion is prevented by haloperidol and pimozide (Schlechter and Butcher, 1972; Rolinski and Scheel-Krüger, 1973). As distinct from the mixed dopamine D-1/D-2 (like apomorphine) and selective dopamine D-2 receptor agonists (like quinpirole) (Arnt et al., 1988), modafinil neither produced stereotypies in mice nor oral stereotypies or low component stereotypies in rats. Moreover, at low and medium doses, it did not potentiate amphetamine-induced stereotyped behaviour in rats and only at very high doses did it slightly increase this behaviour (Ernst, 1967; Vasse et al., 1988). In this respect, our results provide evidence that modafinil differs from amfonelic acid (Aceto et al., 1970), amphetamine, methylphenidate (Scheel-Krüger, 1971), apomorphine (Puech et al., 1975), nomifensine (Braestrup and Scheel-Krüger, 1976) and bupropion (Cooper et al., 1980).

In keeping with the relationship between hyperlocomotion and arousal, preliminary EEG studies in the cat (Jouvet, personal communication), demonstrated that modafinil had vigilance-enhancing properties. Taken together, these results suggest that drug-induced hyperlocomotion linked to a direct or indirect specific activation of central α_1-adrenoceptors could be considered as predictive of potential stimulating activity. In fact, pharmacoclinical (Benoit et al., 1987; Goldenberg, 1986; Goldenberg et al., 1987) and clinical studies (Bastuji and Jouvet, 1986; Billiard et al., 1987; Garma et al., 1986; Laffont et al., 1987; Picard et al., 1986) have confirmed the stimulating influence of modafinil on vigilance in normal or sleep-deprived human subjects and have demonstrated the therapeutic efficacy of modafinil in narcolepsy and idiopathic hypersomnia.

In conclusion, the modafinil-induced hyperlocomotor activity in mice and increased wakefulness in monkeys seem to be dependent upon central α_1-adrenoceptor activity without participation of the dopaminergic system. The absence of peripheral sympathetic effects is noteworthy.

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