Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice

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Abstract

Previously established dose-response curves indicated that modafinil 20–40 mg/kg i.p. elicited in mice an obvious stimulation of locomotor activity roughly similar to that induced by (+)amphetamine 2–4 mg/kg. The effects of various agents modifying dopamine transmission were compared on the locomotor response to both drugs. The preferential D2 dopamine receptor antagonist haloperidol 37.5–150 μg/kg i.p. suppressed the stimulant effect of (+)amphetamine in a dose dependent manner, but not that of modafinil. The D1 dopamine receptor antagonist SCH 23390 (7.5–30 μg/kg s.c.) reversed the (+)amphetamine but not the modafinil induced hyperactivity. The tyrosine hydroxylase inhibitor α-methyl-para-tyrosine (200 mg/kg) suppressed the hyperactivity induced by 4 mg/kg dexamphetamine but not that induced by 20 mg/kg modafinil. Associating L-DOPA 150 mg/kg and benserazide 37.5 mg/kg with (+)amphetamine 2 mg/kg resulted in stereotyped climbing behavior, that was not observed with modafinil 10–80 mg/kg. The profound akinesia induced by reserpine (4 mg/kg s.c.; 5 h before testing) was reversed by (+)amphetamine 2 mg/kg but not by modafinil 40 mg/kg. Finally, on synaptosomes prepared from mouse striata preloaded with [³H]dopamine, modafinil 10^{-5} M did not increase the spontaneous [³H]dopamine release whereas (+)amphetamine, at the same concentration, doubled it. From all these differences between the two drugs, it is concluded that the mechanism underlying the modafinil induced stimulant locomotor effect differs completely from that of (+)amphetamine.

1. Introduction

Modafinil (Modiodal®; diphenyl-methyl-sulfinyl-2-acetamide) stimulates wakefulness and constitutes the therapeutic reference in the treatment of narcolepsy and idiopathic hypersomnia (Bastuji and Jouvet, 1988; Billiard et al., 1988). Administered to various strains of either mice or rats it induces a marked stimulation of locomotion (Simon et al., submitted), whose intensity is comparable to that of the reference psychostimulant drug dexamphetamine (Simon et al., 1994). The hyperactivity induced by dexamphetamine depends on its internalization by dopamine neurons owing to the dopamine carrier. This triggers the release of the newly synthesized cytosolic pool of dopamine (Kamal et al., 1981), thus inverting the way

of the dopamine neuronal transport. Dexamphetamine was also used for treating narcolepsy, but its peripheral and central effects, such as tachycardia, hypertension, tolerance, dependence, anorexia, 'amphetaminic psychosis' and anxiety, have promptly discredited its use. Therefore the development of a new drug must imperatively prove that its mechanism of action differs from that of amphetaminics. A recent report by Mignot et al. (1994) has drawn attention to the apparent neuronal dopamine uptake inhibition elicited by high modafinil concentrations (in the 10^{-5} range). That could correspond either to a pure dopamine uptake inhibition or to a releasing effect of the cytosolic pool of neuronal dopamine, leading to a dopamine release simultaneously with its uptake (Bonnet et al., 1984). This redoubled the interest to investigate modafinil as regards dopamine transmission. Comparing the two drugs, we observed that modafinil does not share the anxiogenic effect of dexamphetamine (Simon et al., 1994). The aim of the

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present study was to complete this comparison by studying the effect of various agents modifying dopaminergic transmission on the locomotion induced by either dexamphetamine or modafinil, in order to show whether they proceed from a similar neurobiological mechanism.

2. Experimental procedures

2.1. Animals

Male Swiss albino mice (Charles River CD1, Saint Aubin lès Elbeuf, France), weighing 20–25 g were used. They were kept under standard conditions: 20 mice per cage (l = 40 cm, w = 25 cm, h = 18 cm), constant temperature (22 ± 1°C), a 12-12 h day-night cycle (lights on from 8 a.m. to 8 p.m.), food and water ad libitum up to the time of the experiment. The experiments were carried out between 10 a.m. and 5 p.m. Each animal was used only once.

2.2. Locomotor activity

Locomotor activity was measured with a Digiscan actimeter (Omnitech Electronics Inc., Columbus, OH, USA). The individual boxes (l = 20 cm, w = 20 cm, h = 30 cm) were placed in a dimly lit room. The horizontal activity was expressed by the total number of beams crossed by mice during the experiment.

2.3. Climbing behavior

Mice were introduced into cylindrical cages (12 cm diameter, 14 cm high) with walls consisting of vertical bars, covered with a smooth surface. All the experimental device was painted black. Measurements were carried out using an image analysis system (Videotrack 512, ViewPoint, Lyon, France). It consisted of four video cameras positioned in front of the experimental field (each one viewing four animals in four cages), a video interface and a microcomputer. The system converted the video input signals into binary images in such a manner that each animal corresponded to a white spot against a black background. Each cage was divided into two virtual areas: the lower one (h = 3 cm) and the upper one which corresponded to the climbing area.

2.4. Synaptosomal preparations

A crude synaptosomal fraction (S1) was obtained by homogenization of the striatum (Potter-Elvehjem, clearance 80–130 μm) in 10 volumes of ice-cold 0.32 M sucrose containing pargyline (0.1 mM), followed by

centrifugation (1000 × g, 10 min, 2°C). The supernatant corresponds to the synaptosomal preparation (S1).

2.5. [^{3}H]Dopamine release medium

The Krebs-Ringer phosphate buffer (NaCl 103 mM, CaCl$_2$ 1 mM, MgCl$_2$ 1 mM, KH$_2$PO$_4$ 1 mM, NaHCO$_3$ 27 mM, glucose 5.4 mM) was gassed (95% O$_2$, 5% CO$_2$) during the superfusion experiments. The K$^+$ induced depolarization was performed by the addition of 40 mM KCl.

2.6. Synaptosomal release of [^{3}H]dopamine

The release of [^{3}H]DA was determined on synaptosomes previously loaded with [^{3}H]DA. For this purpose, 400 μl of S1 suspended in 3500 μl of Krebs-Ringer was incubated for 10 min, at 37°C, in the presence of 100 μl of [^{3}H]DA (100 nM final concentration). The [^{3}H]DA loading was stopped by centrifugation (7000 × g, 10 min, 4°C), followed by a resuspension of the pellet in 1 ml Krebs-Ringer medium and by a second centrifugation to remove unbound, extracellular radioactivity. The pellet was resuspended in 1 ml Krebs-Ringer buffer (S2). The release was measured in a modified superfusion system originally described by Raiteri et al. (1974). Synaptosomal samples S2 were aspirated and 75 μl of S2 was placed on Sartorius filters (0.45 μm). Every superfusion chamber (13 mm diameter, Swinnex, Millipore) containing filters and S2, placed at 37°C, was continuously superfused for 10 min with Krebs-Ringer buffer containing 1 mM K$^+$, to allow equilibration. The release was induced by a medium with the composition described in the legends of the figures. The chamber was perfused with a peristaltic pump at a flow of 0.5 ml/min. One minute, during which the buffer temperature was raised to 37°C, was necessary for the buffer to reach the chamber. Fractions of the superfusate (0.5 ml/min) were collected in scintillation vials (Packard) every min for 15 min. At the end of the superfusion, the radioactivity of each fraction as well as that remaining on the filters, collected in the vials, was measured in 4 ml scintillation fluid (Packard) by liquid scintillation counter (Kontron Betamatic V). The amount of [^{3}H]DA released during 1 min is expressed as the percentage of the total radioactivity. Total radioactivity is equal to the radioactivity released for 25 min of superfusion (including the 10 min for equilibration) plus that remaining on the filter at the end of the experiment. The protein concentration was determined by the method of Lowry et al. (1951).

2.7. Statistics

Statistical comparisons between groups were made with an ANOVA. Statistical comparisons of different groups to control groups were made with Dunnett's *t*-test. Statistical comparisons between two groups were made with Student's *t*-test.

2.8. Drugs

Dexamphetamine sulfate (CPF, Melun, France) was dissolved in saline. Modafinil (a generous gift of Laboratoire L. Lafon, Maisons-Alfort, France), SCH 23390 (Schering Corp., Bloomfield, NJ, USA), α-methyl-*p*-tyrosine (RBI, Natick, MA, USA) and reserpine (Sigma, St. Louis, MO, USA) were dissolved in dimethyl sulfoxide (DMSO) and then diluted in distilled water and Cremophor EL (BASF, Ludwigs-hafen, Germany) (final concentration: 5% DMSO and 5% Cremophor EL). Haloperidol (Haldol®, Janssen Pharmaceutica, Beerse, Belgium) was diluted in saline. L-DOPA–benserazide (Modopar®, Roche, Neuilly sur Seine, France) was suspended in sodium carboxy-methyl-cellulose (water suspension 1%), [^{3}H]dopamine (12 Ci/mmol) was obtained from Amersham (Les Ulis, France).

All drugs were injected in a volume of 10 ml/kg. Indicated doses refer to free base.

3. Results

In a previous study (Simon et al., 1994) it appeared that in mice modafinil (20–40 mg/kg i.p.) significantly stimulated the locomotor activity similarly to (+)amphetamine (2–4 mg/kg i.p.).

The D1 dopamine receptor antagonist SCH 23390 (7.5–30 μg/kg s.c.) suppressed the stimulant locomotor effect of (+)amphetamine (2 mg/kg s.c.) for all tested doses, but was only effective against that of modafinil (40 mg/kg s.c.) for the highest tested dose (Table 1).

The D2 dopamine receptor antagonist haloperidol (37.5–150 μg/kg i.p.) suppressed the stimulant locomotor effect of dexamphetamine (2 mg/kg s.c.) but was ineffective (no significant interaction) towards modafinil (40 mg/kg s.c.) (Table 2).

In mice pretreated with α-methyl-*p*-tyrosine (100 mg/kg i.p. + 100 mg/kg s.c.), a significant reduction in locomotor activity occurred. (+)Amphetamine administered at the 4 mg/kg s.c. dose, which displayed a stimulant locomotor effect in saline pretreated mice, did not reverse the α-methyl-*p*-tyrosine induced reduction of locomotion. On the contrary, modafinil administered at the 40 mg/kg s.c. dose, which increased significantly locomotor activity, reversed the

Table 1
Effect of SCH 23390 on the increase in locomotor activity induced by amphetamine and by modafinil

| | SCH 23390 (μg s.c.) | | | |
	0	7.5	15	30
Solvent	4498 ± 332	2760 ± 440*	2362 ± 314*	1336 ± 213*
Amphetamine	8479 ± 609*	5225 ± 623	3665 ± 668	1046 ± 225
Modafinil	6923 ± 422*	4972 ± 692	4479 ± 607	2010 ± 280

Mice were injected s.c. with solvent (0) or increasing doses of SCH 23390 (7.5, 15 and 30 μg/kg). Ten minutes later they were injected with dexamphetamine 2 mg/kg s.c. or modafinil 40 mg/kg s.c. Fifteen minutes later they were introduced into the actimeter and the locomotor activity was assessed by the number of beams crossed during 30 min. Means ± SEM of nine mice per group.
Comparisons to control group (Dunnett's test): *$P = 0.05$.
Interactions (ANOVA): SCH 2339 × amphetamine: $F = 7.65$ (df: 3,64), $P < 0.001$.
SCH 23390 × modafinil: $F = 2.34$ (df: 3,64), $P > 0.05$.

Table 2
Effect of haloperidol on the increase in locomotor activity induced by amphetamine and by modafinil

| | Haloperidol (μg/kg s.c.) | | | |
	0	37.5	75	150
Solvent	4352 ± 282	2833 ± 411*	2949 ± 395*	1966 ± 682*
Amphetamine	7505 ± 774*	4525 ± 637	3198 ± 199	1694 ± 246
Modafinil	6738 ± 516*	5188 ± 358	5201 ± 401	3955 ± 376

Mice were injected i.p. with solvent (0) or increasing doses of haloperidol (37.5, 75 and 150 μg/kg). Ten minutes later they were injected with dexamphetamine 2 mg/kg s.c. or modafinil 40 mg/kg s.c. Fifteen minutes later they were introduced into the actimeter and the locomotor activity was assessed by the number of beams crossed during 30 min. Means ± SEM of 8–20 mice per group.
Comparisons to control group (Dunnett's test): *$P = 0.05$.
Interactions (ANOVA): haloperidol × amphetamine: $F = 3.94$ (df: 56,63), $P < 0.005$.
haloperidol × modafinil: $F = 0.14$ (df: 56,63), $P > 0.05$.

α-methyl-*p*-tyrosine induced reduction of locomotion (Fig. 1).

The total duration of spontaneous climbing behavior in mice, during the 1 h following drug administration, was significantly increased only by modafinil 40 mg/kg. In mice pretreated with L-DOPA (150 mg/kg) + benserazide (37.5 mg/kg), the climbing behavior became stereotyped (long duration of each episode) only when it was associated with dexamphetamine (Table 3).

In mice pretreated with reserpine (4 mg/kg s.c., 5 h before testing), a complete akinesia occurred. Dex-amphetamine administered at the 2 mg/kg s.c. dose, which displayed a stimulant locomotor effect in saline pretreated mice, obviously reversed the reserpine induced akinesia. On the contrary modafinil adminis-tered at the 40 mg/kg s.c. dose, which also displayed a stimulant locomotor effect in saline pretreated mice, did not at all reverse the reserpine induced akinesia (Fig. 2).
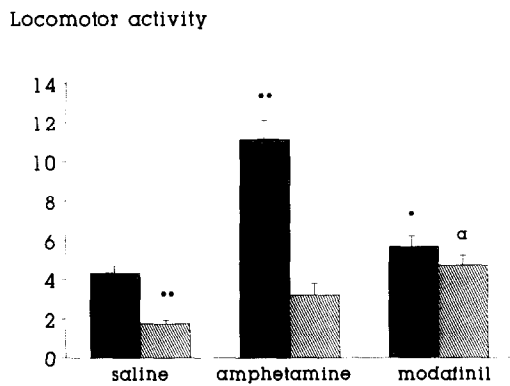
Locomotor activity

Fig. 1. Effect of α-MPT on the increase in locomotor activity induced by amphetamine and modafinil. Mice were injected (s.c. + i.p.) with solvent or α-MPT 200 mg/kg. 210 min later they were injected with solvent (i.p.) or dexamphetamine (4 mg/kg i.p.) or modafinil (40 mg/kg i.p.). 15 min later they were introduced into the actimeter and the locomotor activity was assessed by the number of crossed beams during 30 min. Means ± SEM of eight mice per group. Comparisons to solvent group (Dunnett's test): *P < 0.05. Comparison to α-MPT treated mice (Student's t-test): ^{a}P < 0.001.
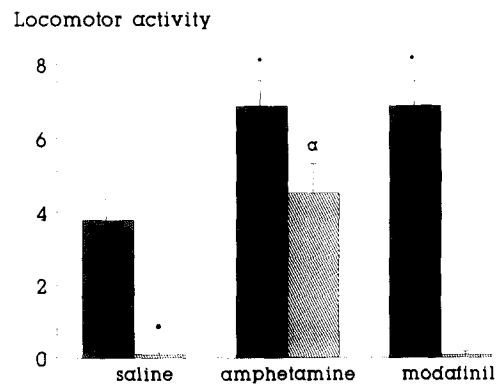
Locomotor activity

Fig. 2. Effect of reserpine on the increase in locomotor activity induced by amphetamine and modafinil. Mice were injected i.p. with solvent or reserpine 4 mg/kg. Five hours later they were injected with solvent (i.p.) or dexamphetamine (4 mg/kg i.p.) or modafinil (40 mg/kg i.p.). Fifteen minutes later they were introduced into the actimeter and the locomotor activity was assessed by the number of crossed beams during 30 min. Means ± SEM of eight mice per group. Comparisons to solvant group (Dunnett' s test): *P < 0.05, **P < 0.01. Comparison to reserpine treated mice (Student's t-test): ^{a}P < 0.001.

On synaptosomes (prepared from mouse striata) preloaded with [^{3}H]dopamine, dexamphetamine (10^{-5} M) induced the release of the [^{3}H]amine, whereas modafinil (10^{-5} M) did not (Fig. 3).

4. Discussion

The stimulant locomotor effect of modafinil arises from a neurobiological mechanism not yet identified.

Its obvious intensity is close to that of dexamphetamine. Both drugs have been used successfully for treating narcolepsy-cataplexy and idiopathic hypersomnia, but, on account of many deleterious effects reported for dexamphetamine, it seemed important to determine whether modafinil displays an amphetamine-like mechanism of action.

Haloperidol, which blocks D2 dopamine receptors (Creese et al., 1975) in a dose dependent manner, antagonized the stimulant effect of (+)amphetamine,
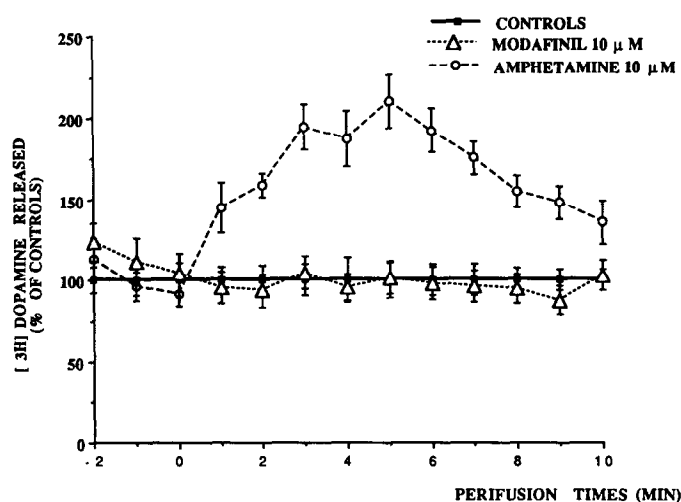
Table 3
Effects of dexamphetamine and modafinil on climbing behavior in mice pretreated with L-DOPA

	Total climbing duration (s)	Mean climbing duration (s)
Saline–saline	699 ± 152	4.8 ± 0.7
Saline–L-DOPA–benserazide	56 ± 28**	2.7 ± 1
Dexamphetamine–saline	978 ± 183	3.5 ± 0.7
Dexamphetamine–L-DOPA–benserazide	2391 ± 190†	11.5 ± 2.0†
Modafinil 10–saline	926 ± 217	6.1 ± 1.5
Modafinil 10–L-DOPA–benserazide	126 ± 98	3.2 ± 1.7
Modafinil 20–saline	948 ± 124	4.0 ± 0.6
Modafinil 20–L-DOPA–benserazide	470 ± 229	3.0 ± 1.3
Modafinil 40–saline	1627 ± 211**	8.9 ± 2.0
Modafinil 40–L-DOPA–benserazide	82 ± 54	3.8 ± 2.6
Modafinil 80–saline	1304 ± 177*	8.0 ± 2.9
Modafinil 80–L-DOPA–benserazide	771 ± 306	4.5 ± 1.1

Mice were injected with: solvent i.p. and saline s.c.; solvent i.p. and amphetamine 2 mg/kg s.c.; solvent i.p. and increasing doses of modafinil (10, 20, 40 and 80 mg/kg s.c.); L-DOPA 150 mg/kg benserazide 50 mg/kg i.p. and saline s.c.; L-DOPA 150 mg/kg benserazide 37.5 mg/kg i.p. and amphetamine 2 mg/kg s.c.; or L-DOPA 150 mg/kg benserazide 37.5 mg/kg i.p. and increasing doses of modafinil (10, 20, 40 and 80 mg/kg s.c.). Twenty minutes after these injections, mice were introduced into the cages. The total climbing duration and the mean climbing duration were measured during the following hour. Means ± SEM of nine animals per group.
Comparisons to solvent group (Dunnett's test): *P < 0.05; **P < 0.01.
Interaction (L-DOPA × amphetamine): †P < 0.001.

Fig. 3. Effect of modafinil or amphetamine on synaptosomal [^{3}H]dopamine release. Synaptosomes were loaded for 10 min, at 37°C, with [^{3}H]dopamine (100 nM final concentration), then they were transferred to superfusion chambers (Millipore). Synaptosomes were superfused for 18 min with a Krebs-Ringer medium for equilibration, at 37°C at a rate of 0.5 ml/min. They were superfused for 10 min in the presence of modafinil (10 μM), or amphetamine (10 μM). The released radioactivity was collected each minute. Means ± SEM of three experiments. Each experiment was performed in triplicate.

whereas it was not able to prevent the stimulant effect of modafinil. Similar observations were made in NMRI mice by Duteil et al. (1990) and Rambert et al. (1990). The former authors did not reverse the stimulant locomotor effect of modafinil 128 mg/kg i.p. by haloperidol for doses up to 0.5 mg/kg i.p., and the latter did not reverse its effects by sulpiride i.p. for doses up to 128 mg/kg. In the same way, in cats, Lin et al. (1992) did not reverse by haloperidol 0.5 mg/kg the wakefulness (electroencephalographically registered) elicited by modafinil. Such a dissociation was less evident when the blockade of D1 dopamine receptors by increasing doses of SCH 23390 (Ioro et al., 1983) was considered. An antagonism was indeed obtained for the two drugs, although higher doses of SCH 23390 were required to antagonize the effect of modafinil compared to those antagonizing the effect of dexamphetamine. This antagonism of the modafinil effect, occurring for relatively low doses of SCH 23390, for which the specificity of action on D1 dopamine receptors is likely, could indicate that dopamine transmission is at least partially involved in the modafinil locomotor effect.

The inhibition of tyrosine hydroxylase by α-methyl-p-tyrosine is known to inhibit the dexamphetamine induced hyperlocomotion. This is the consequence of the depletion of the new synthesized cytosolic pool of dopamine, which is released by dexamphetamine. The persistence of the stimulant effect of modafinil, in spite of this pretreatment, indicates that the drug does not release the cytosolic pool of dopamine. This difference is confirmed by the experiments performed on synaptosomes prepared from mouse striata. As a matter of fact synaptosomes loaded with

[^{3}H]dopamine released the [^{3}H]amine in response to (+)amphetamine (10^{-5} M), whereas in the presence of modafinil (10^{-5} M) they did not release the [^{3}H]dopamine. This observation is in accordance with the in vivo voltammetry studies performed by de Séréville et al. (1994). They indicate that, in anesthetized mice, modafinil did not increase the striatal extracellular level of dopamine and DOPAC after treatment with the MAOI pargyline whereas dexamphetamine increased it.

The treatment with L-DOPA associated with benserazide (at a dose inhibiting the peripheral DOPA decarboxylase activity) which induces a repletion of the dopamine stores, and especially the cytosolic one, potentiated the dexamphetamine effect on the climbing behavior. This stereotyped climbing is reported as the consequence of an intense dopamine transmission in the striatum (Protais et al., 1976), since after L-DOPA administration, dexamphetamine releases more dopamine. Such a potentiation was not at all observed with modafinil, which again excludes the involvement of the cytosolic pool of dopamine in its action.

The treatment with reserpine, which causes a depletion of the vesicular store of the monoamines dopamine, noradrenaline and serotonin, results in a virtually complete akinesia. As is well known, this akinesia is reversed by (+)amphetamine, since the efficacy of the drug is independent of this vesicular store of dopamine. The reserpine induced akinesia was not at all reversed by modafinil, which also indicates the non-involvement of cytosolic dopamine in the stimulant action of modafinil.

In conclusion, although the antagonism by a relatively high dose of SCH 23390 of the hyperlocomotion

elicited by modafinil does not make it possible to exclude the involvement of dopamine transmission in this respect, there is clear evidence that the mechanism of action of modafinil completely differs from that of dexamphetamine. The involvement of a not yet defined subtype of α1-noradrenergic receptors in the modafinil induced wakefulness suggested by Duteil et al. (1990) and Lin et al. (1992) remains an attractive hypothesis.

Acknowledgement

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