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The vigilance promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of a local GABAergic mechanism

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Abstract

The present in vivo microdialysis study demonstrated that the subcutaneous injection of modafinil (diphenyl-methyl-sulfinyl-2-acetamide) in doses of 30–300 mg/kg dose dependently increased dopamine release from the intermediate level of the nucleus accumbens along the rostro-caudal axis of the halothane anaesthetized rat. The effect of modafinil in a dose of 100 mg/kg was counteracted by the local perfusion in the nucleus accumbens with the $GABA_B$ receptor antagonist phaclofen (β-*p*-chlorophenyl-γ-aminopropyl-phosphonic acid) (50 μM), the $GABA_A$ agonist muscimol (3-hydroxy-5-aminomethyl-isoxazolol) (10 μM) and the neuronal GABA reuptake inhibitor SKF89976A (4,4-diphenyl-3-butenyl-nipecotic acid) (0.1 μM), whereas it was increased by the $GABA_B$ receptor agonist (−)-baclofen [β-(*p*-chlorophenyl-γ-aminobutyric acid)] (10 μM). In addition, the modafinil-induced increase of dopamine release was associated with a significant reduction of accumbens GABA release. These results suggest that the dopamine releasing action of modafinil in the rat nucleus accumbens is secondary to its ability to reduce local GABAergic transmission, which leads to a reduction of $GABA_A$ receptor signaling on the dopamine terminals.

Keywords: GABA (γ-aminobutyric acid); Dopamine release; Modafinil; Microdialysis; Nucleus accumbens

1. Introduction

In 1988 Bastuji and Jouvet demonstrated that modafinil (2-diphenyl-methyl-sulphinyl-2-acetamide) may be used for the treatment of hypersomnia in narcoleptic patients (Bastuji and Jouvet, 1988). Furthermore, the vigilance promoting effect of modafinil compared favourably with that of *d*-amphetamine in the treatment of narcoleptic patients by producing less tolerance and less cardiovascular actions. Pharmacological studies in mice and rats by Rambert et al. (1990) also indicate that unlike amphetamine modafinil does not initiate dopaminergic behaviours in rats such as stereotypies and locomotor activity, although vigilance is increased (Duteil et al., 1990). These results suggested that modafinil may possess a reduced abuse potential compared with amphetamine, since the drug abuse potential of psychostimulants appear to be related to their ability to increase dopamine release (Koob and Bloom, 1988). Recently, an hypothesis that the vigilance promoting action of modafinil is related to an inhibitory effect of this drug on γ-aminobutyric acid (GABA) release in the cerebral cortex has been introduced (Tanganelli et al., 1992). To more fully evaluate the GABA involvement in the effects of the psychoactive drug, the GABA/dopamine interactions have been analysed after modafinil treatment in the nucleus accumbens but not in the neostriatum, since dopamine is postulated to exert its rewarding action in the former region (Koob and Bloom, 1988). The halothane anaesthetized model was

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chosen in view of our previous work using this experimental approach (Tanganelli et al., 1994).

In the present experiments involving microdialysis at the intermediate level of the nucleus accumbens along the rostro-caudal axis, it is demonstrated that acute administration of modafinil (100–300 mg/kg s.c.) increases accumbens dopamine release and reduces accumbens GABA release. Furthermore, evidence is given that the modafinil-induced increase of dopamine release may be directly mediated by a reduction of local GABA release in this brain region, leading to a reduction of $GABA_A$ receptor signalling on the dopamine terminals.

2. Materials and methods

2.1. Animals

Male adult Sprague-Dawley rats (300–350 g body weight) were used in the present study. They were kept under a 12 h light/dark cycle (lights on at 6 a.m.) and in a temperature-controlled environment with free access to water and food.

2.2. Microdialysis procedures

The animals, anaesthetized with a 1.5% mixture of halothane and air, were mounted in a David Kopf stereotaxic frame with the upper incisor bar set at −2.5 mm below the interaural line. A microdialysis probe of concentric design (0.5 mm O.D.; 2 mm length) was stereotaxically implanted into the intermediate nucleus accumbens according to the following coordinates: A: +1.5; L: 1.5; V: −7.6, from the bregma and the dura, respectively (Paxinos and Watson, 1982). During the surgery, the probe was perfused with Ringer solution at a constant flow rate of 2 μl/min by a microinfusion pump (CMA 100, Carnegie Medicin, Sweden).

The anaesthesia was maintained throughout the microdialysis experiment by free breathing into a mask fitted over the nose of the rat and the body temperature was kept constant at 37°C. The collection of samples started 2 h after the probe implantation and the perfusates were collected every 20 min. After three stable basal values had been obtained, modafinil was subcutaneously injected. When required, a local 60 min perfusion with the $GABA_B$ receptor antagonist phaclofen (β-*p*-chlorophenyl–aminopropylphosphonic acid) (Kerr et al., 1987; Krebs et al., 1993), the $GABA_B$ receptor agonist (−)-baclofen [β-(-*p*-chlorophenyl-γ-aminobutyric acid)] (Bowery et al., 1980; Hill and Bowery, 1981), the neuronal GABA reuptake blocker SKF89976A (4,4-diphenyl-3-butenyl-nipecotic acid) (Yunger et al., 1984), the $GABA_A$ receptor agonist muscimol (3-hydroxy-5-aminomethylisoxazolol) (Bowery et al., 1984; Sieghart, 1989) and the $GABA_A$ receptor antagonist bicuculline 6-(5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)furol[3,4-*e*]-benzodioxol-8(6*H*)-one (Bowery et al., 1984; Sieghart, 1989) was performed. The addition of any of the compounds used in this study did not affect the pH of the perfusion medium as well as the qualitative and quantitative HPLC assays of dopamine and GABA standard solutions containing the relevant compounds. The in vitro recovery for dopamine and GABA was 22 ± 3% and 18 ± 4%; respectively.

2.3. Analytical procedures

2.3.1. Dopamine measurement

The amount of dopamine in each dialysate sample was assayed by direct injection (40 μl of the perfusates) into a reverse phase high performance liquid chromatography (HPLC) column (C18, Spherisorb 5 m, 100 × 3 mm Chrompak). The system was based on a Kontron dual piston pump, an electrochemical detector (Biometra) and a Softron-PC integrator. The mobile phase consisted of 0.15 mM sodium phosphate, 0.1 mM EDTA, 0.6 mM sodium octane sulphonate and 17% methanol adjusted to pH 3.8 and pumped at a flow rate of 0.5 ml/min. The limit of detection was 10 fmol for dopamine per sample. The concentration of the monoamine detected in the dialysate samples was determined by comparison with external standard solutions of dopamine.

2.3.2. GABA measurement

The GABA analysis used in this study was previously described by Kehr and Ungerstedt (1989). The amount of GABA in each dialysate sample was assayed by direct injection (10 μl of the perfusates) into a reverse phase high performance liquid chromatography. Briefly, the method is based on a precolumn derivatization with an *o*-phthaldialdehyde/*t*-butylthiol reagent and separation by reverse-phase HPLC on a Nucleosil 3 (C18) column with electrochemical detection under isocratic conditions. The mobile phase consisted of 0.15 mM sodium acetate, 0.1 mM EDTA, pH 5.4 and 50% acetonitrile. The flow rate of the mobile phase was 0.8 ml/min. The limit of detection for GABA was 20 fmol/sample. The concentration of the amino acid detected in the dialysate samples was determined by comparison with external standard solutions of GABA.

2.4. Statistical analysis

The data were reported as percentage of the mean of the three basal samples collected before treatment. The area value created by the curve, mainly reflecting the duration of the effect under the 120 min period, was calculated for each animal and expressed as percentage changes in arbitrary units. The statistical analysis was carried out by one-way factorial analysis of variance (ANOVA) followed by Newman-Keuls test for multiple comparisons. The minimum level for statistical significance was set at $P < 0.05$.

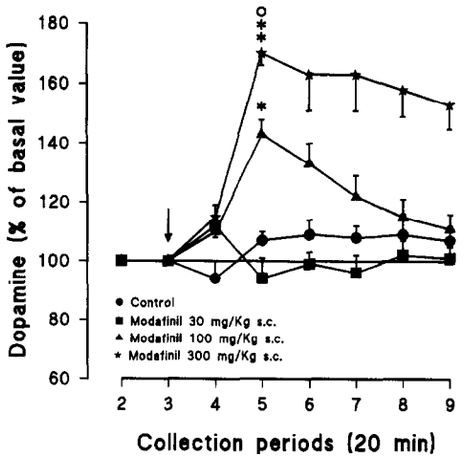

Fig. 1. Effects of modafinil (30, 100 and 300 mg/kg s.c.) on dopamine release from the nucleus accumbens of the halothane-anaesthetized rat. The changes in dopamine release are expressed as percentages of the mean of the three basal values. Basal dopamine levels in 40 μl were 0.1030±008 pmol. Each data point represents the mean ± S.E.M. of 5–7 animals. The arrow indicates the injection of the vehicle or the drug. The area under the curve values (arbitrary units) are: control = 906±345; modafinil (30 mg/kg) = 460±179; modafinil (100 mg/kg) = 2971±478 **; modafinil 300 (mg/kg) = 7214±698 ^{**,oo}. The significance for the peak effect is indicated. The statistical analysis was carried out according to a one-way ANOVA analysis followed by Newman-Keuls test for multiple comparisons. * $P < 0.05$, ** $P < 0.01$ vs. control and modafinil (30 mg/kg); ^{o} $P < 0.05$, ^{oo} $P < 0.01$ vs. modafinil (100 mg/kg).

2.5. Drugs

Fresh solutions of the following drugs were used: (−)-baclofen (Ciba Geigy, Basel, Switzerland), Phaclofen (Tocris Neuramin, Buckurst Hill, Essex, UK) SKF89976A [4,4-diphenyl-3-butenyl-nipecotic acid] (Smith Kline and French, Welwyn, UK), muscimol, (−)-bicuculline methochloride (Sigma Chemical Company, St Louis, MO, USA. Modafinil (L. Lafon, Maisons Alfort, France) was suspended in a 0.5% arabic gum solution. This vehicle was injected to control animals.

3. Results

3.1. Basal perfusate accumbens dopamine levels

The basal values for dopamine in 40 μl perfusate samples were 0.10 pmol (see text to figure legends). The absolute value in saline-treated animals and in the vehicle-treated animals were identical and remained stable throughout the release experiment.

3.2. Effects of modafinil on accumbens dopamine release

As shown in Fig. 1, the acute subcutaneous administration of modafinil (100 mg/kg) rapidly increased dopamine release, reaching the peak effect (+43% of basal values) 40 min after the injection. The dopamine release then gradually declined to pretreatment level by the end of the experiment (120 min). The administration of a very high dose of modafinil 300 mg/kg, produced a consistent and long-lasting increase in dopamine release, which was still present at the end of the collection period. At a lower dose of 30 mg/kg modafinil did not affect basal dopamine release.

3.3. Effects of manipulation of local GABA transmission on modafinil-induced accumbens dopamine release

The facilitation of dopamine release in the nucleus accumbens induced by modafinil (100 mg/kg) was studied under conditions of local perfusion (60 min) with compounds which are known to interfere with GABAergic transmission.

3.3.1. Phaclofen plus modafinil

As shown in Fig. 2A, the addition to the perfusion medium of the $GABA_B$ receptor antagonist phaclofen (50 μM), fully counteracted the modafinil-induced increase of dopamine release.

3.3.2. (−)-Baclofen plus modafinil

Local perfusion with the $GABA_B$ receptor agonist (−)-baclofen (10 μM) enhanced the facilitatory effects of modafinil (100 mg/kg) on dopamine release. The increase induced by (−)-baclofen in combination with modafinil was maximal 40 min after drug administration and was higher (+78% of basal values) than that observed for modafinil alone (Fig. 2B). In addition, the time course of the enhancement of dopamine release observed during this combined treatment was more prolonged and only returned to basal values 120 min after the cessation of perfusion with (−)-baclofen (data not shown).

3.3.3. SKF89976A plus modafinil

Interestingly, local perfusion with the selective inhibitor of neuronal GABA reuptake SKF89976A (0.1 μM) fully counteracted the modafinil-induced increase of dopamine release in the accumbens (Fig. 2C).

All treatments performed with the above compounds interfering with GABA transmission were ineffective with regard to dopamine release when perfused alone (Table 1).

3.3.4. Bicuculline and muscimol

Local perfusion with the $GABA_A$ antagonist bicuculline (50 μM) for 60 min into the intermediate nucleus accumbens significantly increased dopamine release, reaching the peak action 60 min after the onset of the perfusion. Following the washout of bicuculline the dopamine release returned to the basal levels (Fig. 3A). On the contrary, muscimol (50 μM), locally perfused for 60 min, significantly decreased basal dopamine release (Fig. 3A). At a lower concentration (10 μM) the $GABA_A$ agonist did not affect accumbens dopamine release (Fig. 3B).

3.3.5. Muscimol plus modafinil

As shown in Fig. 3B the local perfusion with muscimol (10 μM) fully antagonized the modafinil-induced increase of dopamine release.

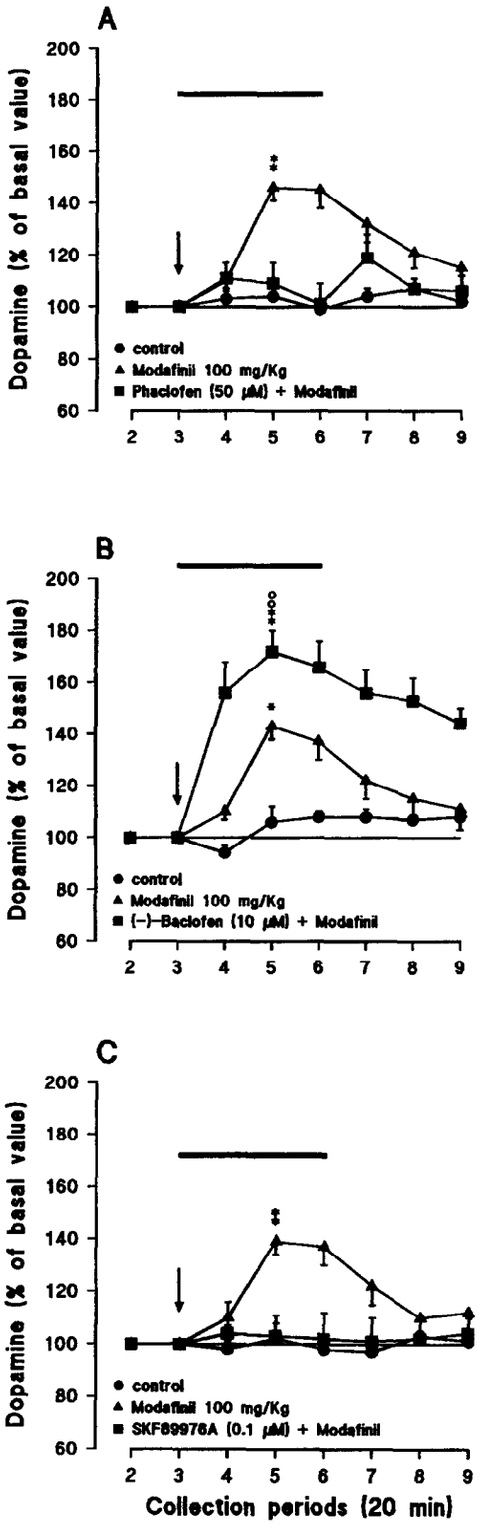

Table 1
Effects of phaclofen, (−)-baclofen and SKF89976A on dopamine release from the nucleus accumbens of the halothane-anaesthetized rat

Collection period	Control	Phaclofen 50 μM	(−)-Baclofen 10 μM	SKF89976A 0.1 μM
1–3	100	100	100	100
4	98±3	91±6	107±6	100±2
5	102±2	97±9	105±7	109±5
6	104±6	95±6	105±6	106±3
7	99±3	102±8	96±7	99±3
8	106±5	100±7	98±7	105±2
9	102±4	100±5	97±6	103±3

The drugs were locally perfused through the accumbens for 60 min (vertical black bars). The data are expressed as percentages of the mean of the three basal values collected before treatment. Each data point represents the mean±S.E.M. of 4–5 rats.

3.4. Effects of modafinil on accumbens GABA release

In view of the above results and previous findings indicating that modafinil in the cerebral cortex reduces GABA outflow and that dopamine transmission in the accumbens is under a GABAergic inhibitory control, we also tested the hypothesis whether the enhancement of dopamine release induced by modafinil could be mediated by a reduction of GABA release.

Thus, the effects of modafinil (30, 100 and 300 mg/kg s.c.) were studied by analysing simultaneously both accumbens GABAergic and dopaminergic transmission. In this way, it was possible to correlate in the same animal the changes induced by the drug on GABA and dopamine release at the same time. As shown in Fig. 4, the injection of modafinil (100 and 300 mg/kg) produced a dose-dependent reduction of GABA release within the accumbens, the lower dose (30 mg/kg) being ineffective. At both the

Fig. 2. (A,B,C) Effects of modafinil (100 mg/kg s.c.) alone and in the presence of (A) a $GABA_B$ receptor antagonist phaclofen (50 μM); (B) a $GABA_B$ receptor agonist (−)-baclofen (10 μM) and (C) an inhibitor of neuronal GABA reuptake SKF89976A (0.1 μM) on dopamine release from the nucleus accumbens of the halothane-anaesthetized rat. The drugs, were locally perfused through the nucleus accumbens for 60 min (black bars). The arrows indicate when modafinil was injected. The results are expressed as percent of the mean of the three basal values. Basal dopamine levels in 40 μl were 0.0950±006 pmol. Each data point represents the mean±S.E.M. of 6–7 animals. The area under the curve values (arbitrary units) are: (A) control = 556±145; modafinil = 3114±480 **; phaclofen plus modafinil = 943±287. ** $P<0.01$: significantly different from control and modafinil plus phaclofen groups. (B) control = 682±201; modafinil = 2996±424 *; (−)-baclofen plus modafinil = 7182±744 ^{**,oo}. * $P<0.05$; ** $P<0.01$: significantly different from control; ^{oo} $P<0.01$ significantly different from modafinil. (C) control = 451±125; modafinil = 2874±480 **; SKF89976A plus modafinil = 486±103. ** $P<0.01$: significantly different from control and modafinil plus SKF89976A groups. The significance for the peak effect is indicated. The statistical analysis was carried out according to a one-way ANOVA analysis followed by Newman-Keuls test for multiple comparisons.

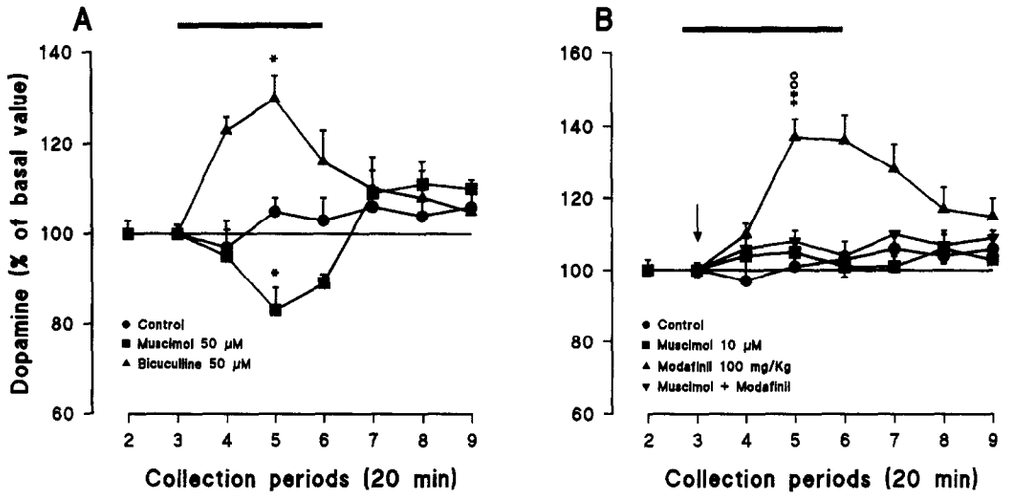

Fig. 3. (A) Effects of the $GABA_A$ receptor antagonist bicuculline (50 μM) or the $GABA_A$ receptor agonist muscimol (50 μM) on dopamine release from the nucleus accumbens of the halothane anaesthetized rat. (B) Effects of modafinil (100 mg/kg s.c.) alone and in the presence of muscimol (10 μM) on dopamine release from the nucleus accumbens of the halothane-anaesthetized rat. The drugs were locally perfused through the nucleus accumbens for 60 min (black bars). The arrow (B) indicates when modafinil was injected. The results are expressed as percent of the mean of the three basal values. Basal dopamine levels in 40 μl were 0.1110 + 007 pmol. Each data point represents the mean ± S.E.M. of 5–6 animals. The area under the curve values (arbitrary units) are: (A) control = 944 ± 366; bicuculline = 2272 ± 398 **; muscimol = −301 ± 86 **; * $P < 0.05$; ** $P < 0.01$: significantly different from control group. (B) control = 987 ± 133; muscimol = 388 ± 154; modafinil = 2994 ± 398 ^{**,oo}; muscimol + modafinil = 898 ± 121 ** $P < 0.01$: significantly different from control as well as muscimol alone groups; ^{oo} $P < 0.01$: significantly different from muscimol plus modafinil-treated group. The significance for the peak effect is indicated. The statistical analysis was carried out according to a one-way ANOVA analysis followed by Newman-Keuls test for multiple comparisons.

active doses, GABA release returned to the basal values 120 min after drug administration. As expected, the evaluation of dopamine release showed a dose-dependent increase. The effects induced by the different concentrations of modafinil (100–300 mg/kg) were analysed. A linear regression relationship between the enhancement of dopamine release and the reduction of GABA release was found for the dose of 100 mg/kg (dopamine = −2.61 · GABA + 361; $r^2 = 0.805$; $P < 0.05$). However, this correlation was no longer present with the higher dose (300 mg/kg).

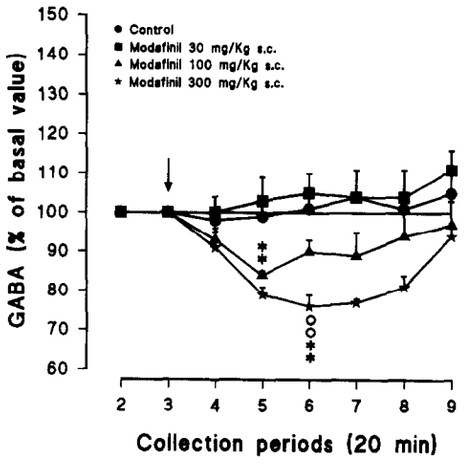

Fig. 4. Effects of modafinil (30, 100 and 300 mg/kg s.c.) on GABA release from the nucleus accumbens of the halothane-anaesthetized rat. The changes on GABA release are expressed as percentages of the means of the three basal values. Basal GABA levels in 40 μl were 0.6530 ± 060 pmol. Each data point represents the mean ± S.E.M. of 7 animals. The arrow indicates the injection of the vehicle or the drug. The area under the curve values (arbitrary units) are: control = 392 ± 88; modafinil (30 mg/kg) = 540 ± 145; modafinil (100 mg/kg) = −1131 ± 258 **; modafinil 300 (mg/kg) = −2404 ± 132 ^{**,o}. The significance for the peak effect is indicated. The statistical analysis was carried out according to a one-way ANOVA analysis followed by Newman-Keuls test for multiple comparisons. ** $P < 0.01$ vs. control and modafinil (30 mg/kg); ^{o} $P < 0.05$, ^{oo} $P < 0.01$ vs. modafinil (100 mg/kg).

4. Discussion

In the present study we demonstrate that modafinil (100–300 mg/kg s.c.) dose dependently increases dopamine release from the intermediate nucleus accumbens of the halothane-anaesthetized rat. The facilitation induced by the 100 mg/kg dose of the drug is counteracted by local perfusion with the $GABA_B$ receptor antagonist phaclofen, the $GABA_A$ receptor agonist muscimol and the neuronal GABA reuptake inhibitor SKF89976A, whereas it is increased by the $GABA_B$ receptor agonist (−)-baclofen. Thus, the ability of modafinil to increase dopamine release within the nucleus accumbens appears to be mediated by local GABAergic systems. The involvement of local GABA neurons may be explained as follows. The counteraction of the modafinil-induced increase of dopamine release by local application of the $GABA_B$ antagonist phaclofen could be due to the blockade of a

presynaptic $GABA_B$ receptor (Karlsson et al., 1988; Deisz et al., 1993) leading to a reduction in the autoinhibition feedback mechanism, resulting in an enhancement of the GABA release with increases in GABA levels which, in turn, activate $GABA_A$ receptors (see below) on local dopamine terminals and thus reduce dopamine release (Krebs et al., 1993). In agreement with this explanation are the findings that the local perfusion with the GABA uptake blocker SKF89976A (Yunger et al., 1984) also counteracts the increase in dopamine release probably by increasing extracellular GABA levels. In contrast, the $GABA_B$ receptor agonist (−)-baclofen enhances the facilitation of dopamine release induced by modafinil. This action can be explained on the basis that (−)-baclofen activates $GABA_B$ autoreceptors leading to reduced GABA release (Uchimura and North, 1991) and a reduced activation of GABA receptors on dopamine terminals (Pickel et al., 1988; Wachtel and Andén, 1978; Tanganelli et al., 1994). The observation that, at the concentrations used, the above drugs did not affect basal dopamine release seems to indicate that the modafinil-induced inhibition of GABA release sensitizes the $GABA_B$ autoreceptor function, possibly contributing to a higher sensitivity of these receptors to the actions of the $GABA_B$ agonist and antagonist used. In line with this explanation, Waldmeier et al. (1993) has recently demonstrated that in striatal slices, GABA autoreceptor function operates only at low stimulation intensity.

The demonstration that local perfusion with the $GABA_A$ agonist muscimol fully counteracts the effect of modafinil on dopamine release strengthens the hypothesis that the increase in dopamine release in the nucleus accumbens induced by modafinil (100 mg/kg) could be a consequence of local inhibition of GABA release. Thus, by increasing $GABA_A$ tone on the dopamine terminals through local muscimol perfusion, the action of modafinil is counteracted. The presence of a local ($GABA_A$-mediated) tonic inhibitory control by GABA neurons of dopamine nerve terminals in the nucleus accumbens, already demonstrated in our previous study (Tanganelli et al., 1994), is confirmed by the increase of dopamine release observed following the perfusion with bicuculline (50 μM) alone as well as by the reduction of dopamine release induced by muscimol (50 μM) alone. An inhibitory GABA-dopamine interaction also operates at the nigral level, since Santiago and Westerink (1992) demonstrated that intranigral infusion of bicuculline (50 μM) increased dopamine release in the ipsilateral striatum of awake rats. Furthermore, at the level of prefrontal cortex the local perfusion of picrotoxin increased dopamine release (Santiago et al., 1993) suggesting the existence of a GABA/dopamine interaction also at the cortical level (Fuxe et al., 1975, 1977).

The involvement of GABAergic mechanisms in the modafinil-induced increase of accumbens dopamine release is further demonstrated by the reduction of accumbens GABA release observed after modafinil administration. A similar inhibitory action of this psychoactive drug on GABA release has been shown in other brain regions such as the cerebral cortex (Tanganelli et al., 1992), the medial preoptic area and the posterior hypothalamus (Tanganelli et al., 1995). In view of the fact that GABA has been shown to play a major role in sleep mechanisms through inter alia actions in the two latter areas (Lin et al., 1989; Sallanon et al., 1989) it seems possible that the reduction in regional GABA release by modafinil may be one mechanism underlying the vigilance-promoting action of the drug. Finally, the lack of a significant correlation between inhibition of GABA release and increase of dopamine release at the higher dose of 300 mg/kg of modafinil may be related to other actions of the drug such as dopamine uptake inhibition found at higher concentrations (Fuxe et al., 1992; Mignot et al., 1994).

In view of the above, the modest dopamine releasing action of modafinil in the nucleus accumbens found at lower doses appears to be secondary to its ability to reduce local GABAergic transmission. In view of its indirect nature, the modafinil-induced increase in dopamine release unlike the direct dopamine release caused by amphetamine and amphetamine-like drugs is not expected to lead to dependence (Carlsson et al., 1966; Koob and Bloom, 1988). However, the indirect enhancement of dopamine transmission within the nucleus accumbens by modafinil in a dose of 100 mg/kg may nevertheless facilitate activity in locomotor and reward networks in this region.

In conclusion, the present findings indicate that the manners in which modafinil promotes vigilance may differ from the conventional psychostimulant drugs of the amphetamine type which directly act to increase dopamine release (Carlsson et al., 1966), a factor which may explain its lack of dependence-producing effects. These findings, demonstrating increases of dopamine release via inhibition of GABA release, open up the possibility for the use of modafinil and its analogues in the treatment not only of hypersomnolence, but also of Parkinson's disease, known to be caused by deficits of dopamine transmission, and of certain forms of depression which are thought to reflect a low tone of the dopamine reward system. Together with the previously demonstrated neuroprotective actions of modafinil (Fuxe et al., 1992) these data suggest that modafinil may represent a new type of antiparkinsonian drug capable of producing both acute relief of symptoms and delay of the degeneration processes in dopamine neurons.

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