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Lack of Pre-synaptic Dopaminergic Involvement in Modafinil Activity in Anaesthetized Mice: *In Vivo* Voltammetry Studies

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Summary—Modafinil was compared to the indirect dopaminergic drugs, dexamphetamine and methylphenidate, using *in vivo* differential normal pulse voltammetry with carbon fibre electrodes located in the caudate nucleus to study extracellular catechol level in anaesthetized mice. Modafinil (16–256 mg kg^{-1}) failed to modify the catechol oxidation peak height (peak 2). Dexamphetamine at low doses (2 and 4 mg kg^{-1}) decreased, while at a higher dose (8 mg kg^{-1}) did not modify peak 2 height. A low dose of methylphenidate (16 mg kg^{-1}) did not display any effect, while higher doses (32 and 64 mg kg^{-1}) increased peak 2 height. Pargyline-induced monoamine oxidase inhibition elicited a rapid and dramatic decrease in peak 2 height (related to the decrease of catechol levels). In these conditions modafinil (64 and 256 mg kg^{-1}) did not modify, while dexamphetamine (2, 4 and 8 mg kg^{-1}) and methylphenidate (16, 32 and 64 mg kg^{-1}) increased peak 2 height in relation to synaptic dopamine level increase. This study, in mice, demonstrated the lack of effects of modafinil on nigro-striatal function, at the pre-synaptic level, as opposed to dexamphetamine and methylphenidate.

Keywords—Voltammetry, anaesthetized mice, dopamine, modafinil, dexamphetamine, methylphenidate.

Electrochemical technique has been applied to monitor catecholamines (Lane *et al.*, 1978; Gonon *et al.*, 1978) and indolamines (Cespuglio *et al.*, 1980) in brain tissue *in vivo*. In spite of a lack of specificity, this technique is useful to follow neuronal function. Differential normal pulse voltammetry used in conjunction with electrically treated pyrolytic carbon fibre microelectrodes (Gonon *et al.*, 1981a, 1984) is able to separate ascorbic acid (AA) from catechols (Gonon *et al.*, 1981b).

The relative participation of catechols, dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC), generally used to study dopaminergic function *in vivo* (Stamford, 1986), was demonstrated by pharmacological investigations (Gonon *et al.*, 1984). Continuous monitoring of extracellular dopamine or DOPAC level as an index of dopaminergic metabolism (Gonon *et al.*, 1980, 1981b; Maidment and Marsden, 1985) could be achieved by *in vivo* voltammetry. This method originally described in the rat, was adapted to mice, and allowed to assess the nigro-striatal pre-synaptic dopaminergic function after administration of drugs like modafinil, dexamphetamine and methylphenidate, which were reported to induce hyper-locomotor activity in this species. Modafinil is a new drug which was reported to increase locomotor activity without stereotypy in mice (Duteil *et al.*, 1990b), nocturnal activity in monkeys (Hermant *et al.*, 1991) and awakening in cats (Lin *et al.*, 1992) through non-dopaminergic mechanisms. In fact, modafinil-induced hyperactivity and awakening were prevented by the centrally acting alpha-1 adrenergic antagonists prazosin and phenoxybenzamine but not by the preferential D2 dopaminergic antagonists sulpiride, haloperidol (Duteil *et al.*, 1990b; Hermant *et al.*, 1991; Lin *et al.*, 1992) or by the preferential D1 dopaminergic antagonist SCH 23390 (Costentin, personal communication). In contrast, hyper-locomotion elicited in mice by dexamphetamine or methylphenidate, both of which known to induce hyper-locomotor activity and stereotyped behaviour (Scheel-Krüger, 1971) through an increased synaptic dopamine level, was prevented by D1 and D2 dopaminergic antagonists (Costentin, personal communication) but not by the alpha-1 adrenergic antagonist prazosin (Rambert *et al.*, 1990). Moreover, the catecholamine synthesis inhibitor, alpha methyl para tyrosine, did not reduce modafinil- but prevented dexamphetamine-induced hyper-locomotor activity in mice (Duteil *et al.*, 1990b; Hermant *et al.*, 1991) and

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awakening in cats (Lin *et al.*, 1992). A preliminary account of this work has previously been presented (Duteil *et al.*, 1990a).

METHODS

Animals

Mice (male, NMRI, CER Janvier), weighing 35–40 g were used. They were housed at 22 ± 1.5°C in home cages under a 12 hr light/12 hr dark cycle (light on from 6 a.m. to 6 p.m.) and had free access to food and water. Experiments were conducted at room temperature (21 ± 1.5°C).

Experimental procedures

All experiments were carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). All efforts were made to minimize animal suffering and to reduce the number of animals used.

Animals were anaesthetized with chloral hydrate (400 mg kg^{-1}, i.p.) under a volume of 20 ml/kg body weight and set in a stereotaxic frame (Société Réalisation et Applications Mécaniques). Further doses of anaesthetic (5 mg kg^{-1}, i.p.) were given when necessary to maintain anaesthesia at a level sufficient to abolish hind limb withdrawal reflexes.

Working carbon fibre electrodes (Ponchon *et al.*, 1979) were implanted according to coordinates from Lehmann (1974) in mice left caudate nucleus (A: 5.0, L: 1.6, H: +3.3 mm). The reference and the auxilliary electrodes were placed on the occipital skull surface.

Following a 30–60 min stabilization, recordings were started and continued over 3 hr after drug administration.

Animals were assigned to treatment groups using a randomized complete block design (Lellouch and Lazar, 1974). Drugs were administered i.p. in a volume of 20 ml/kg body weight. Doses of basic compounds refer to the salts. Control animals always received the same number of injections of the appropriate volume of the respective excipient (deionized water for amphetamine and methylphenidate, 0.005% gum arabic solution for modafinil) at the corresponding time intervals.

When monoamine oxidase (MAO) inhibition was required, pargyline (96 mg kg^{-1}, i.p.) was injected in mice, 90 min before drugs.

At the end of experiment an anodic potential (5 V, 5 sec) was applied at working electrode. Animals were sacrificed with an overdose of chloral hydrate. After decapitation, the brain was removed, frozen and sectioned to verify the electrode placement.

Electrochemical procedures

Voltammetric measurements were performed using a classical three electrodes system. The reference electrode was a conventional Ag/AgCl electrode filled with NaCl 3 M; the auxilliary electrode was made of platinum. The working electrodes (Gonon *et al.*, 1978; Ponchon *et al.*, 1979), made of one carbon fibre (dia. 8 μm, length 800 μm, Carbone Lorraine), were electrically treated (Gonon *et al.*, 1980, 1981a) before each experiment by applying a triangular wave potential (0 to +2.95 V, 70 Hz, 20 sec) followed by two continuous potentials (−0.8 V, 5 sec then +1.5 V, 10 sec) in phosphate buffer solution. The electrode system was driven by a Biopuls voltammograph (Tacussel, France) connected to an Ecoscript recorder (Tacussel, France).

The following electrochemical parameters were used: potential range −180 +210 mV, potential step 2 mV, pulse period 0.2 sec, prepulse duration 80 msec, pulse duration 40 msec, scan rate 10 mV sec^{-1}, pulse amplitude 20 mV. Differential normal pulse voltammograms were recorded every 2.5 min.

Before and after each *in vivo* experiment, microelectrodes were calibrated in a phosphate buffered saline solution containing 200 μM ascorbic acid and 10 or 20 μM DOPAC (Gonon *et al.*, 1981b).

Drugs

Ascorbic acid (Sigma), dopamine hydrochloride (Sigma), DOPAC (Sigma), were dissolved in phosphate buffer saline solution (KCl, 0.2 g l^{-1}; NaCl, 0.8 g l^{-1}; $Na_2HPO_4 \cdot 2H_2O$, 1.44 g l^{-1}; KH_2PO_4, 0.2 g l^{-1}; pH 7.4).

Chloral hydrate (Prolabo), pargyline hydrochloride (Sigma), dexamphetamine sulfate (Coopération Pharmaceutique Française), methylphenidate (Ciba), were dissolved in deionized water; modafinil (Lafon) was suspended in a 0.005% arabic gum solution.

Data analysis

Drug effects were assessed by the difference between catechol oxidation peak height (peak 2) at each time and peak 2 height at time 0 min. Means (±SEM) of the treated groups were compared with the appropriate control group using Dunnett's test (SYSTAT software), following an analysis of variance (ANOVA) with repeated measures, assessment of the variance homogeneity (Bartlett's test) and of the normality of the distributions. A P value of 0.05 was accepted as the level of statistical significance.

RESULTS

Modafinil

Modafinil, at all the doses studied, displayed no modification in peak 2 height excepted between 30 and 90 min (64 mg kg^{-1}) and 60 and 90 min (256 mg kg^{-1}) where a slight, but significant, decrease was observed (Fig. 1). A significant time effect [$F(17,459) = 11.058$, $P < 0.001$] was noted, but without treatment effect [$F(2,27) = 2.656$, $P = 0.088$] and treatment × time interaction [$F(34,459) = 1.309$, $P = 0.118$], as a consequence of a similar slight decrease in the peak 2 height with time, whatever the treatment.

After pargyline-induced monoamine oxidase inhibition (MAOI), peak 2 was dramatically reduced and in these conditions modafinil was devoid of any relevant effect (Fig. 2); time effect [$F(17,459) = 3.901$, $P < 0.001$] and treatment × time interaction [$F(34,459) = 14.721$, $P < 0.001$] were statistically significant, while treatment effect [$F(2,27) = 1.830$, $P = 0.180$] was not, as a consequence of a slight decrease in peak 2 height with time in control and modafinil 64 mg kg^{-1}, opposed to a slight increase in modafinil 256 mg kg^{-1}.

Dexamphetamine

With dexamphetamine, at the lowest doses used (2 or 4 mg kg^{-1}), a slight but statistically significant decrease in peak 2 height was maximal after 90 min and lasted over 3 hr; at the highest dose used (8 mg kg^{-1}), no modification of peak 2 height was observed (Fig. 1). Treatment effect [$F(3,16) = 9.471$, $P < 0.001$], time effect [$F(17,272) = 19.669$, $P < 0.001$] and treatment × time interaction [$F(51,272) = 4.921$, $P < 0.001$] were statistically significant, as a consequence of peak 2 height variations in different ways according to the dose. Following pargyline, a weak electrochemical signal was observed, and the addition of dexamphetamine (2, 4 or 8 mg kg^{-1}) induced an increase in peak 2 height, maximal between 50 and 100 min and lasting up to 3 hr (Fig. 2). Treatment effect [$F(3,16) = 3.554$, $P = 0.0241$ and time effect [$F(17,612) = 3.352$, $P < 0.001$] were s' istically significant, but without treatment × time interaction [$F(51,612) = 1.188$, $P = 0.180$], as a consequence of increase in peak 2 height with time, whatever the dose.

Methylphenidate

Methylphenidate, at the lowest dose (16 mg kg^{-1}), did not evoke any effect but at higher doses (32 or 64 mg kg^{-1}) produced a marked increase in peak 2 height; this effect was maximal by 30–40 min and lasted 2 to 3 hr (Fig. 1). Treatment effect [$F(3,16) = 4.188$, $P = 0.023$], time effect [$F(17,272) = 9.830$, $P < 0.001$] and treatment × time interaction [$F(34,459) = 1.505$, $P = 0.021$] were statistically significant, indicating that peak 2 height was differently modified with time, according to the dose.

Following peak 2 suppression with pargyline, methylphenidate induced a dose-dependent increase in peak 2 height, maximal between 40 and 80 min, lasting up to 3 hr (Fig. 2). Treatment effect [$F(3,16) = 8.783$, $P = 0.003$], time effect [$F(17,272) = 9.485$, $P < 0.001$] and treatment × time interaction [$F(51,272) = 2.311$, $P < 0.001$] were statistically significant, indicating that peak 2 height was differently modified with time, according to the dose.

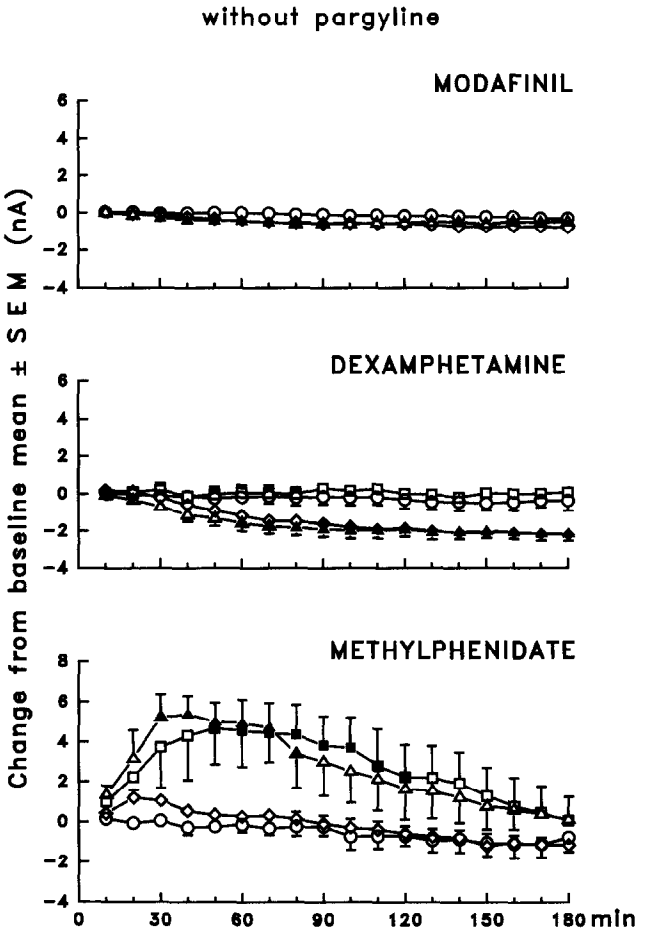

Fig. 1.

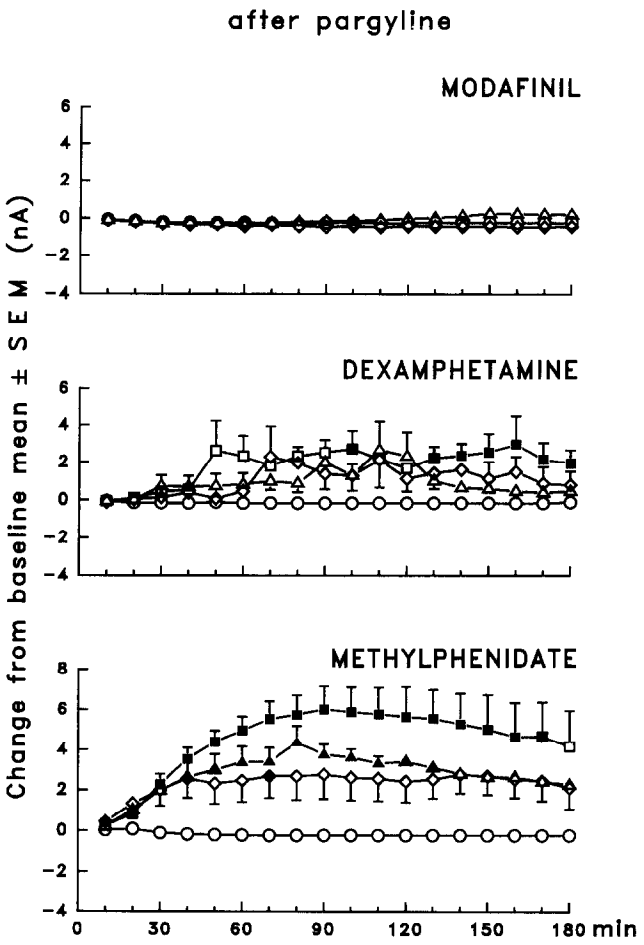

Fig. 2

DISCUSSION

The choice of the species was directed to the mouse since the three drugs, modafinil, dexamphetamine and methylphenidate clearly displayed hyperlocomotor activity in this species (Duteil *et al.*, 1990a) whereas rat is poorly reactive to modafinil. Consequently, the voltammetric technology had to be adapted to the mouse, a species not yet used for this purpose.

Carbon fibre electrodes in combination with differential normal pulse voltammetry appeared as a valuable tool to study *in vivo* dopaminergic neuronal function in brain (Gonon *et al.*, 1984). Separation of ascorbic acid (peak 1) from dopamine and DOPAC (peak 2) can be achieved by electrical pretreatment of graphite paste (Brazell *et al.*, 1982), carbon paste (O'Neill *et al.*, 1982) or carbon fibre (Gonon *et al.*, 1981a) electrodes, the latter was selected in our studies. *In vitro*, dopamine elicited a peak at a potential (+100 mV) close to the DOPAC one (+80 mV). The oxidation current was reported to increase linearly with DOPAC or dopamine concentration, measured with carbon fibre (Gonon *et al.*, 1980) or graphite paste electrodes (Brazell and Marsden, 1982).

In our hands, *in vitro*, in presence of ascorbic acid, oxidation current increased linearly with DOPAC (5–50 μM) or dopamine (0.2–5 μM) concentration.

Thus, so treated electrodes appeared to display higher sensitivity towards dopamine than towards DOPAC (Brazell and Marsden, 1982).

Dopamine and DOPAC are mainly contained in the terminals of dopaminergic neurons, originating from substantia nigra and projecting to caudate nucleus in mice (Andén and Gabrowska-Andén, 1983); moreover it was already reported that DOPAC participation to the catechol peak is prominent compared with dopamine (Gonon *et al.*, 1980).

Animal pretreatment with the MAOI pargyline, which blocks the intraneuronal transformation of dopamine to DOPAC (Westerink and Korf, 1976), suppressed the peak 2 in striatum and nucleus accumbens of anaesthetized rats (Buda *et al.*, 1981). In such conditions, the catechol oxidation peak, recorded after drug administration, was ascribed to dopamine rather than to DOPAC (Gonon *et al.*, 1984). In our study, the peak 2 height remained constant with time in control mice, but was dramatically reduced following MAOI

pretreatment; this is in keeping with previous studies in rats (Gonon *et al.*, 1980).

Modafinil (64–256 mg kg^{-1}) demonstrated a slight variation of peak 2 height which could be related to a different electrode sensitivity (low sensitivity to DOPAC, high sensitivity to dopamine), a decrease in peak 2 height, related to a decrease in DOPAC level, could be balanced by an increase in dopamine level.

However, in MAOI-pretreated animals, modafinil, even at doses as high as 256 mg kg^{-1}, did not enhance the peak 2 height. Therefore a change in dopamine neuronal function does not play a role in the mechanism of action of modafinil.

Dexamphetamine (2–4 mg kg^{-1}) produced an important decrease in peak 2 height. However at the highest dose used (8 mg kg^{-1}) this decrease was absent. This dexamphetamine-induced decrease in peak 2 and DOPAC was already reported in rat studies using voltammetry (Gonon *et al.*, 1980), intracerebral dialysis (Zetterström *et al.*, 1986) or microdialysis (Westerink *et al.*, 1987; Butcher *et al.*, 1988). The dexamphetamine-induced lowering of DOPAC could result from a decrease in the firing of the nigro-striatal neurons, (Zetterström *et al.*, 1986) or from a reversible MAO inhibition as it was demonstrated in rat brain (Miller *et al.*, 1980) and striatal slices (Schoepp and Azzaro, 1982). So, it was hypothesized that dexamphetamine (8 mg kg^{-1}) induced two opposite changes, a decrease in DOPAC formation, and an increase in dopamine release, as a result peak 2 height remained unchanged.

This hypothesis was substantiated by our results in mice demonstrating that, following a MAOI pretreatment which prevented DOPAC formation, dexamphetamine, clearly restored the peak 2, which could only be ascribed to dopamine.

However, low doses of dexamphetamine produced only a statistically not significant increase in peak 2 height. This slight increase in peak 2 height, following low doses of dexamphetamine may be attributed to a low dopamine level, an insufficient dopamine detection by the electrode or a low dopamine release and a rapid inactivation by either pre-, post- or extra-synaptic uptake (Justice *et al.*, 1988) before diffusion to the electrode (Kelly and Wightman, 1987). These results are in keeping with those of other studies using brain dialysis or microdialysis, demonstrating a dexamphetamine-induced dopamine release in rat striatum (Zetterström *et al.*, 1986; Sharp *et al.*, 1987). An other possibility is that the excitation induced by dexamphetamine needs repeated injection of the anaesthetic, affecting the level of arousal of the mice, with concomitant changes in dopamine neuronal neurotransmitter release and electrochemical signal amplitude.

Thus, dexamphetamine effect could result from the combination of at least two actions: on the one hand, a decrease in DOPAC level leading to a reduction of the electrochemical signal, on the other hand, a dopamine release resulting in an increase in dopamine level leading to the enhancement of electrochemical signal.

Methylphenidate, 32–64 mg kg^{-1} without MAOI pretreatment, or 16–64 mg kg^{-1} with MAOI pretreatment, showed a dose-dependent increase in peak 2 height. This increase could be attributed to dopamine rather than DOPAC release, since it was evidenced in non-MAOI- as well as in MAOI-pretreated animals. Methylphenidate, 16 mg kg^{-1}, increased peak 2 height in MAOI-pretreated mice only and the result obtained without MAOI pretreatment may be attributed to a balance between a decrease in DOPAC and an increase in dopamine levels, as suggested for dexamphetamine. An increase in dopamine release was reported with methylphenidate in cats (Chiueh and Moore, 1975) and rats (McMillen, 1983; Duteil *et al.*, 1987), as a consequence of a rapid transfer from a stored to a releasable pool of dopamine.

Striatal dopamine levels were reported to correlate to stereotyped behaviour in mice (Herman, 1975). Accordingly, direct dopaminergic agonists, such as apomorphine (Puech *et al.*, 1975; Ross, 1978), or indirect dopaminergic agonists, such as dexamphetamine (Sharp *et al.*, 1987; Scheel-Krüger, 1971) and methylphenidate (Ross, 1978; Scheel-Krüger, 1971), were reported to elicited stereotyped behaviour in rats.

Then, the results presented demonstrate that, contrarily to dexamphetamine and methylphenidate, modafinil did not interact with the nigro-striatal pre-synaptic dopaminergic function. This is in keeping with the lack of stereotyped behavior observed in mice and rats (Duteil *et al.*, 1990b). Moreover, *in vivo*, modafinil-induced hyperactivity in mice was not antagonized by dopaminergic blocking agents while it was prevented by alpha-1 adrenergic antagonists (Duteil *et al.*, 1990b). Elsewhere, modafinil was unable to modify the firing pattern of the rat dopaminergic (substantia nigra, ventral tegmental area) and noradrenergic (locus coeruleus) neurons while amphetamine consistently inhibited their activity (Akaoka *et al.*, 1991). *In vitro*, modafinil, up to 1 μM, did not display any affinity for the rat striatal dopaminergic D1 and D2 binding sites labelled by [^{3}H]SCH 23390 and [^{3}H]sulpiride, respectively (Mignot, personal communication). Likewise, it did not display any affinity for striatal dopamine uptake complex labelled either by [^{3}H]mazindol (unpublished results) or by [^{3}H]GBR 12783, and up to 10 μM did not increase the release of [^{3}H]dopamine from synaptosomes pre-labelled with the [^{3}H]amine then submitted to superfusion (Costentin, personal communication).

Contrarily, dexamphetamine induced important behavioural changes: on the one hand, a stereotyped behaviour in relation with increased dopamine level in striatum (Costall *et al.*, 1977; Sharp *et al.*, 1987), on the other hand, an hyperlocomotor activity in relation with an increased dopamine level in the nucleus accumbens (Sharp *et al.*, 1987).

Likewise, methylphenidate-induced stereotyped behaviour and hyperlocomotor activity are a consequence of dopamine level increase. This dopaminergic involvement, evidenced by voltammetric and behavioural studies, was reported in microdialysis studies *in vivo* (Sharp *et al.*, 1987) or in rat striatal slices *in vitro* (Dyck *et al.*, 1980).

In conclusion, modafinil did not interact with the nigro-striatal pre-synaptic dopaminergic function as shown by studies in mice using differential normal pulse voltammetry with carbon fibre electrode. In that it differs from dexamphetamine and methylphenidate which produce an increase in dopamine level in caudate nucleus, associated with stereotyped behaviour and hyperlocomotor activity. These data give further evidence to exclude a dopaminergic involvement in the mechanism of modafinil-induced hyperlocomotor activity in mice.

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