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Changes in EEG spectral power in the prefrontal cortex of conscious rats elicited by drugs interacting with dopaminergic and noradrenergic transmission

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1 The electroencephalographic (EEG) effects of drugs interacting with dopaminergic and noradrenergic systems were studied in conscious rats. Power spectra (0–30 Hz) were recorded from electrodes implanted bilaterally in the prefrontal cortex. Drug effects on EEG power were calculated as the spectral power following drug administration divided by the spectral power after vehicle administration.

2 Dopaminergic agonists at low doses, (apomorphine 0.01 mg kg^{-1} s.c., quinpirole 0.01 mg kg^{-1} i.p.) and dopaminergic antagonists (haloperidol 1 mg kg^{-1} i.p., raclopride 2.5 mg kg^{-1} s.c.), which decrease dopaminergic transmission, induced an increase of EEG power. Conversely, dopaminergic agonists at higher doses (apomorphine 0.5 mg kg^{-1} s.c., quinpirole 0.5 mg kg^{-1} i.p.) which increase activation of postsynaptic D_2 and D_3 receptors, induced a decrease of EEG power.

3 The α_1-adrenoceptor antagonists (phenoxybenzamine 0.64 mg kg^{-1} s.c., prazosin 0.32 mg kg^{-1} s.c.) and the α_2-adrenoceptor agonists (UK 14304 0.05 mg kg^{-1} s.c., clonidine 0.025 mg kg^{-1} i.p.), which decrease noradrenergic transmission, induced an increase of EEG power. Conversely, the α_1-adrenoceptor agonist, cirazoline (0.05 mg kg^{-1} s.c.), the adrenergic agent modafinil (250, 350 mg kg^{-1} i.p.) and α_2-adrenoceptor antagonists (RX 821002 0.01 mg kg^{-1} s.c., yohimbine 0.5 mg kg^{-1} i.p.), which increase noradrenergic transmission, induced a decrease of EEG power. The effects of prazosin (0.64 mg kg^{-1} s.c.) were dose-dependently antagonized by co-administration with modafinil and cirazoline, but not by apomorphine.

4 In conclusion, pharmacological modulation of dopaminergic and noradrenergic transmission may result in consistent EEG changes: decreased dopaminergic or noradrenergic activity induces an increase of EEG spectral power; while increased dopaminergic or noradrenergic activity decreases EEG spectral power.

Keywords: Prefrontal cortex; monoamines; modafinil; prazosin; dopamine; EEG

Abbreviation: EEG, electroencephalogram

Introduction

The prefrontal cortex is a key area of the brain coordinating working memory and attention in man and rodents (Ungerleider, 1995; Posner, 1997; Wharton & Grafman, 1998), which is important in several mood disorders and which we have extensively characterized in dialysis studies in the rat (Gobert *et al*., 1998).

Recent advances in EEG methodology have led to marked improvements in the clinical utilization of this diagnostic technique. High resolution EEG has been coupled to magnetic resonance imaging or positon emission tomography (PET) to study cognitive function and attention in man (Gevins *et al*., 1995). Marked differences can be shown in prefrontal and sensorimotor cortex with different forms of cerebral activation, such as spatial or verbal working memory (Gevins *et al*., 1995). In clinical studies, EEG can be used to define changes in the progression of Alzheimer's disease (Miyauchi *et al*., 1994) and depression (Thase *et al*., 1998; Kalayam *et al*., 1998), and differences in comparison with vascular dementia have been reported (Partanen *et al*., 1997). Further, subtle EEG changes may accompany the cerebral microangiopathy associated with severe diabetes (Inui *et al*., 1998). The prefrontal cortex in man is a major site for working memory (Posner, 1997; Rugg *et al*., 1998; Wharton & Grafman, 1998) and Sarnthein *et al*. (1998) have shown that low frequency (7–8 Hz) EEG oscillations interact between the prefrontal cortex and posterior association areas during working memory tasks.

In drug studies, EEG and evoked potentials are extensively used in Phase I and II clinical testing (Hermann *et al*., 1991). Electrophysiological studies have shown that delta wave and spindle activity are inhibited by stimulating noradrenergic neurones and cholinergic nuclei in animals (Steriade *et al*., 1990a; 1991; 1993a,b,c).

We have set up a system to assess the influence of drugs on the EEG in the prefrontal cortex of conscious rats in an attempt to define the changes induced by a spectrum of agents reported to modify vigilance and attention. This study forms part of an extensive characterization of the effects of drugs on the EEG of conscious rats to differentiate the various pharmacological classes and to form a database allowing comparison of drug-evoked changes in animals and humans.

By examining the EEG changes induced by noradrenergic and dopaminergic agonists and antagonists (Sebban *et al*., 1987; Monti *et al*., 1989; Gaillard, 1990; McCormick &

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Williamson, 1991; McCormick, 1992), the principal objective of this paper was to evaluate if general relationships exist between alterations in prefrontal EEG in conscious rats and the functioning of noradrenergic and dopaminergic systems, as described biochemically and behaviourally (Tassin *et al*., 1992; Blanc *et al*., 1994).

Classic modulators of the dopaminergic system (the mixed D_1 and D_2 agonist, apomorphine and the D_2 agonist, quinpirole; D_2 antagonists: haloperidol and raclopride) and the noradrenergic system (α_2-adrenoceptor agonists: UK14304 and clonidine; α_2-adrenoceptor antagonists: RX 821002 and yohimbine; α_1-adrenoceptor agonist: cirazoline; α_1-adrenoceptor antagonists: phenoxybenzamine and prazosin) were used to modulate dopaminergic and noradrenergic transmission at doses established to be maximally effective behaviourally while remaining selective for the receptor of interest (Gobert *et al*., 1998; Millan *et al*., 1998).

Modafinil, an agent which enhances vigilance specifically and which is clinically used for the treatment of narcolepsy (Bastuji & Jouvet, 1988; Besset *et al*., 1993; Boivin *et al*., 1993; Guilleminault *et al*., 1993; Billiard *et al*., 1994; Billiard & Carlander, 1998), was also investigated. Because of its relative innocuity, lack of a direct stimulant effect and a lasting suppression of sleep without apparent rebound, the drug has been proposed for military operations (Lyons & French, 1991). Modafinil has an unknown mechanism of action in that the drug does not bind to α_1-adrenoceptors (although there are many subtypes of α_1-adrenoceptor in the rat cortex, Pieribone *et al*., 1994) but its selective effects on vigilance and the EEG are antagonized by prazosin (Mignot *et al*., 1988a,b; Duteil *et al*., 1990; Jouvet *et al*., 1991; Hermant *et al*., 1991; Lagarde & Milhaud, 1990; Rambert *et al*., 1990; Lin *et al*., 1992). Modafinil does not increase anxiety in mice (Simon *et al*., 1994) but it increases noradrenaline release throughout the cortex (Akaoka *et al*., 1991). Modafinil is less potent in rodents than in higher species, and consequently higher doses (>50 mg kg^{-1} i.p.) have to be used compared with cats and primates (5 mg kg^{-1} i.p.).

Methods

Animals

The study was carried out on male Wistar rats (510 ± 25 g) aged 8 months. They were housed in the laboratory. The rats were submitted to a light period of 12 h and were free to access food and water under controlled environmental conditions ($20 \pm 2^{\circ}$C).

The rats were anaesthetized with chloral hydrate (350 mg kg^{-1} i.p.) and put into a stereotaxic frame. Two holes were drilled bilaterally in the right and left prefrontal regions and two others in the right and left sensorimotor regions (Figure 1A). Four trans-cortical bipolar electrodes were thus inserted. Each electrode had one exposed site on its external part which was placed on the cerebral cortical surface. The second exposed site was on the central tip which was introduced through the cortex. The distance between the two exposure sites was 1 mm. The rats were earthed *via* a stainless steel screw fixed in the frontal bone. After connecting the electrodes and the screw to a connecting plug, they were fixed to the skull by acrylic cement.

Fourteen days later, when rats recovered from the surgical operation, each of them was habituated to remain quiet in a restraining cage which was used during the EEG recording to decrease artifacts of movement. It needed about 10 – 14 days to make the rats adapt to EEG recording without a notable stress reaction.

EEG recording

Fifteen groups of six rats each have been used in this study. In twelve groups, the EEG changes induced by one single drug have been evaluated. According to the studied drug, one, two, three or four doses have been evaluated (see paragraph drugs). When more than one dose has been evaluated, the order of doses was randomly chosen for each rat. Also, a 1 week drug-free interval was imposed between the study of two different doses of the same drug. For prazosin interactions, one group was used for each combination of two drugs.

For each dose, two EEG recordings were performed in each rat. The first recording lasted for 165 min after i.p. injection of vehicle. The second was done 24 h later for the same duration following drug administration. The recordings were obtained at the same time every day to avoid the bias caused by nycthermeral EEG variations. EEG recordings were performed by placing the rat in a restraining cage and then into a large, electrically insulated and acoustically isolated chamber. A light source was present 10 cm in front of the nose of the rat. EEG signals were amplified, filtered (anti-aliasing filters: 90 db/oct) and digitized (64 points/s) for the Fourier transformation which allowed calculation of the

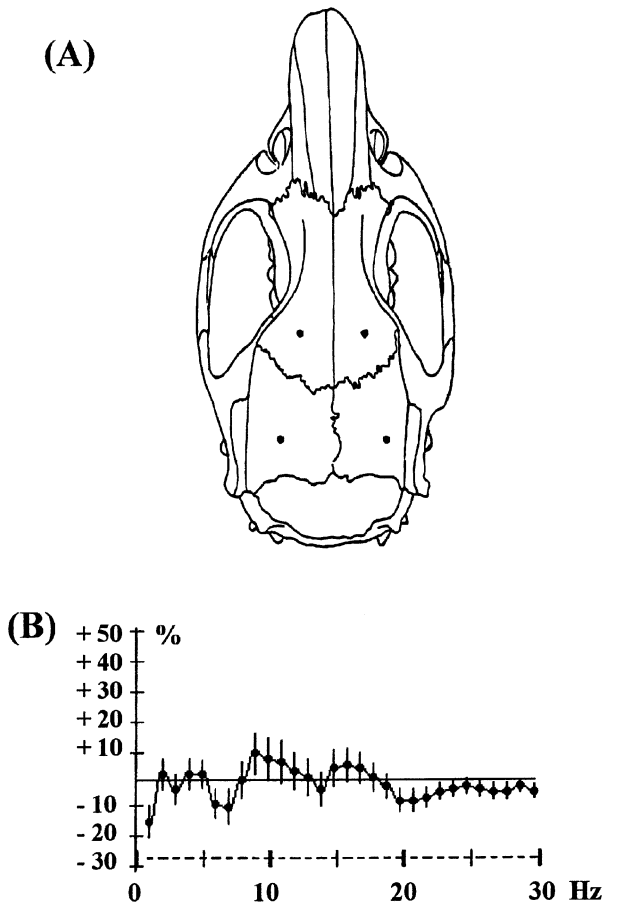

Figure 1 Position of the electrodes in the rat brain (A = +4 mm, L = 2.5 mm for the prefrontal cortex; A = −4 mm, L = 4 mm for the sensorimotor cortex). (B) Stabilities of the recording following two i.p. injections of saline over a 24 h interval. In this and all subsequent figures, the ordinates represent the change in EEG power at each Hz step, expressed as a percentage of the EEG power spectrum obtained with the first injection of vehicle. Vertical bars represent 95% confidence intervals.

power variable (μV^2). Absolute power spectra of EEG signals were computed every 30 s from 1–30 Hz in steps of 1 Hz. In each rat, Hertz by Hertz drug-induced power variations were evaluated by the ratio of power after injection of the drug/power after injection of the vehicle (see below). The EEG spectral power of left and right prefrontal cortex together were averaged for 5 min periods for each recording session.

Drugs

The following investigational drugs were used: Apomorphine (0.01 mg kg^{-1}, 0.5 mg kg^{-1} s.c.; Sigma), quinpirole (0.01 mg kg^{-1}, 0.5 mg kg^{-1} i.p.; RBI), raclopride (2.5 mg kg^{-1} s.c.; RBI), haloperidol (1 mg kg^{-1} i.p.; Sigma), modafinil (150, 200 and 250 mg kg^{-1} i.p.; gift of Laboratoires Lafon), cirazoline (0.05 mg kg^{-1} s.c.; RBI) RX 821002 (0.01 mg kg^{-1} s.c.; RBI), yohimbine (0.1 mg kg^{-1} i.p.; Sigma), UK 14304 (0.01, 0.05 and 0.1 mg kg^{-1} s.c.; RBI), clonidine (0.01, 0.025 and 0.05 mg kg^{-1} i.p.; RBI), phenoxybenzamine (0.64 mg kg^{-1} s.c.; ICN) and prazosin (0.08, 0.16, 0.32 and 0.64 mg kg^{-1} s.c.; Sigma). For the study of prazosin interactions, prazosin (0.64 mg kg^{-1} s.c.) was used with apomorphine (0.01, 0.1 and 0.5 mg kg^{-1} s.c.), modafinil (250 and 350 mg kg^{-1} i.p.) and cirazoline (0.64, 1.25 and 2.5 mg kg^{-1} s.c.). These drugs were administered immediately after prazosin.

Data analysis

The EEG spectral power from prefrontal cortex in the left and right hemispheres were each averaged for 5 min periods for each recording session. Except for apomorphine 0.01 mg kg^{-1} which showed at this dose a rebound in 7–13 Hz between 56–165 min following its administration (Shvaloff *et al.*, 1988), spectral power of 33 successive 5 min periods (165 min) were averaged. For apomorphine 0.01 mg kg^{-1}, we only averaged

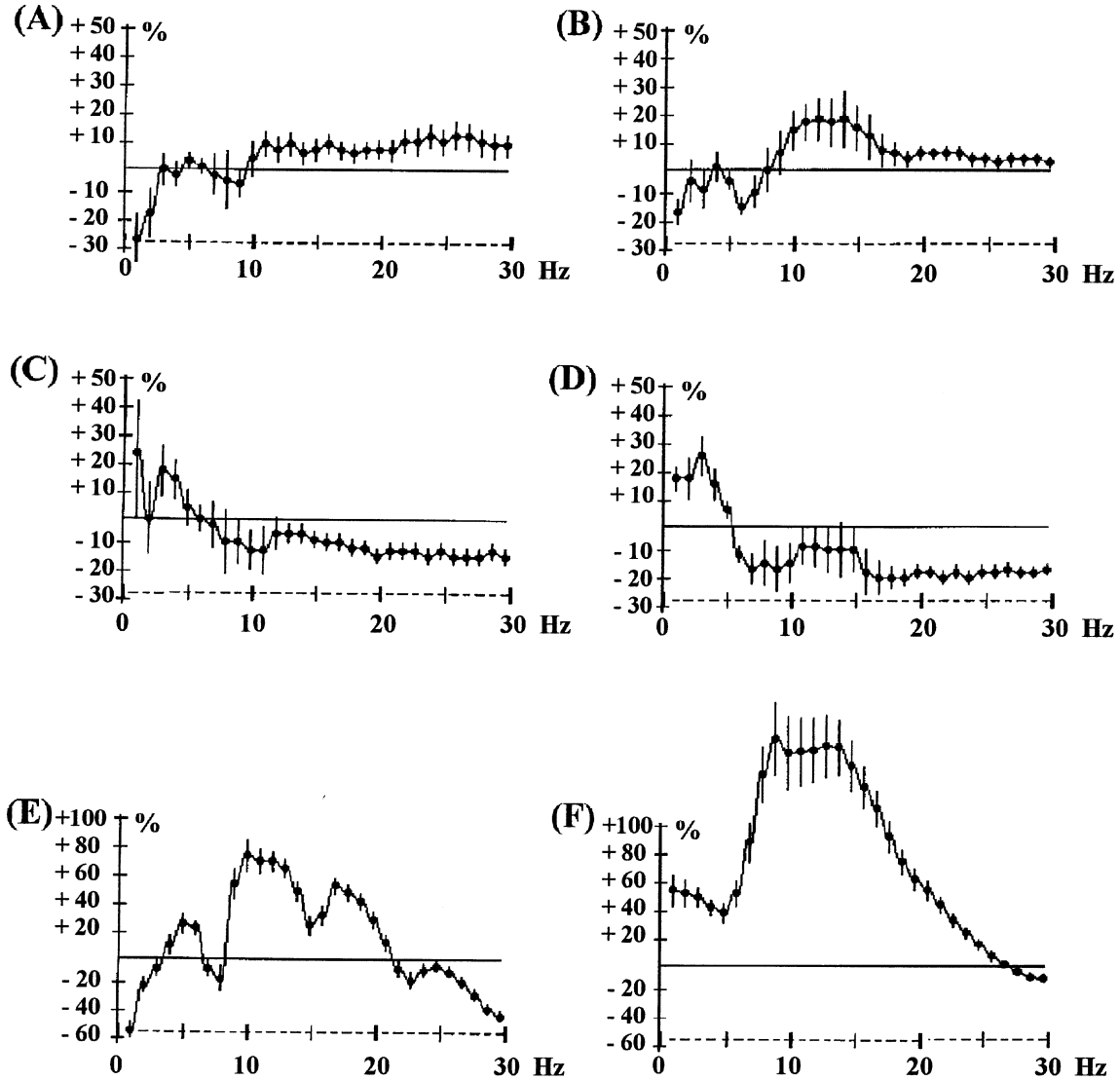

Figure 2 Effects of apomorphine, 0.01 mg kg^{-1} s.c. (A), 0.5 mg kg^{-1} (C); quinpirole 0.01 mg kg^{-1} i.p. (B), 0.5 mg kg^{-1} (D); raclopride, 2.5 mg kg^{-1} s.c. (E) and haloperidol, 1 mg kg^{-1} i.p. (F) on EEG spectral power in the prefrontal cortex in conscious rats. The abscissa represents the EEG spectral component between 1 and 30 Hz. The horizontal line at zero indicates no change. The ordinate indicates the per cent change in the EEG power spectrum produced by drug administration, as a percentage of the EEG spectrum obtained with vehicle administration 24 h earlier. The increases in EEG power may be taken as a synchronization of EEG at the particular frequency and a decrease in power as a desynchronization. Because of local factors (electrode placement) synchronization of the EEG change yields larger per cent changes than desynchronization. Vertical bars for each Hz show 95% confidence intervals ($n=6$).

the first 11 successive 5 min periods. The drug-induced changes in EEG spectral power were calculated as the ratio of mean spectral power obtained following the injection of drug versus the mean spectral power obtained following administration of vehicle:

$$\text{variation of mean spectral power (\%)} = \frac{\text{EEG power following drug}}{\text{EEG power following vehicle}} \times 100$$

This procedure therefore allows for the change in EEG power, at each frequency, expressed as a per cent of the original power, induced by a drug, compared with the control, in the same animal. This ratio was calculated at each 5 min interval after the beginning of recordings.

Statistical analysis

For each dose of drug, ratios describing the drug effects over each 5 min period have been submitted to an analysis of variance (ANOVA) with three main factors: cortical region, time (first, second and third hour with 12 repetitions) and animals. For some drugs where dose-dependency was evaluated, a fourth main factor of dose was introduced. The mean power change for each cortical region was calculated from the number of rats and the time. The confidence intervals were calculated for an α risk less or equal to 0.05. This confidence interval corresponds to the vertical bars in every Figure. $P<0.05$ for each drug effect, regarding an increase or decrease in power, was taken as being significant.

Results

Effects of dopaminergic agonists and antagonists

As shown in Figure 1B, there were no significant changes in EEG power between two recordings separated by 24 h when the rats were administered vehicle.

Both apomorphine and quinpirole showed biphasic dose-related effects on EEG spectral power, generally increasing power at low doses (apomorphine 0.01 mg kg^{-1}, quinpirole 0.01 mg kg^{-1}) and decreasing power at higher doses (apomorphine 0.5 mg kg^{-1}, quinpirole 0.5 mg kg^{-1}). The low dose of apomorphine induced a decreased power for a narrow band (1–3 Hz) and an increased power over 10–30 Hz (Figure 2A). At the low dose (Figure 2B), quinpirole decreased the EEG power of 1–3 Hz as well as 5–7 Hz, and increased power over a broad band (9–18 Hz). At the high dose, both apomorphine and quinpirole induced opposite effects on EEG spectral power. With high doses of apomorphine, an increased EEG power at 1–5 Hz appeared which was associated with a decreased EEG power over 7–30 Hz (Figure 2C). The same shape of spectral changes was observed with quinpirole, which increased EEG power in 1–5 Hz and decreased EEG power in 6–30 Hz (Figure 2D).

Dopamine antagonists, raclopride or haloperidol, increased EEG spectral power. Raclopride (2.5 mg kg^{-1}) increased power in most frequencies except 1–3, 7–8 and more than 22 Hz (Figure 2E). Haloperidol (1 mg kg^{-1}) increased the EEG spectral power over almost all the frequency range, with the maximum effect seen over 9–14 Hz (Figure 2F).

Effects of α_1-adrenoceptor agonists and α_2-adrenoceptor antagonists

Modafinil (250 mg kg^{-1}) decreased EEG power over the frequencies 6–18 Hz (Figure 3A) and the effect was weakly dose-dependent (Figure 6D), but the dose-dependency was significant by ANOVA. The maximum effect was seen at 11 Hz. Cirazoline, an α_1-adrenoceptor agonist, had a different influence on the EEG power profile (Figure 3B). It induced a decreased power at 3, 5–6, 8 and 13 Hz and an increased power at 1–2 and 19–30 Hz.

RX 821002 (0.01 mg kg^{-1}) or yohimbine (0.1 mg kg^{-1}) each induced EEG changes characterized by a decrease of

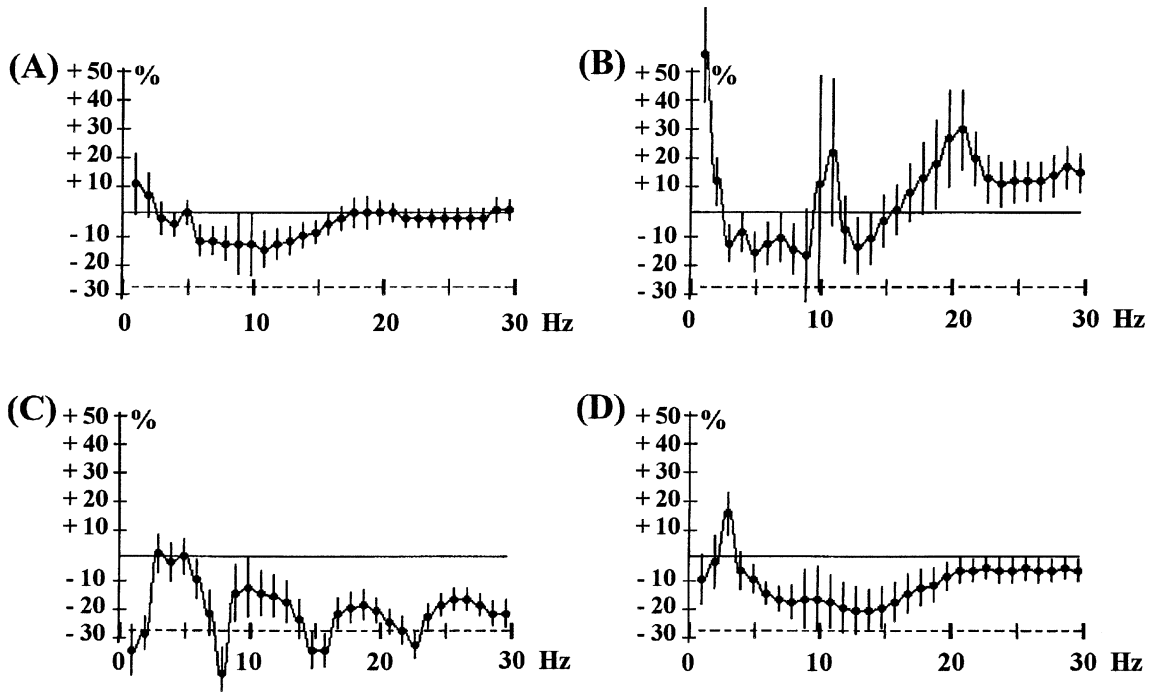

Figure 3 Effects of modafinil 250 mg kg^{-1} i.p. (A), cirazoline 0.05 mg kg^{-1} s.c. (B), RX 821002 0.01 mg kg^{-1} s.c. (C) and yohimbine 0.1 mg kg^{-1} i.p. (D) expressed as per cent change of EEG spectral power in the prefrontal cortex of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals.

EEG power (Figure 3). The spectra of drug-induced change by RX 821002 showed troughs of power at 1, 8, 15 and 23 Hz (Figure 3C). As shown by Figure 3D, yohimbine decreased the EEG power in all the frequencies except 3 Hz. The maximum decrease in power was at 13 Hz.

Effects of α_1-noradrenergic antagonists and α_2-noradrenergic agonists

The α_1-adrenoceptor antagonists, phenoxybenzamine (0.64 mg kg^{-1}) and prazosin (0.32 mg kg^{-1}), increased the power of the EEG. For phenoxybenzamine, this increase was important and highly significant from 8–20 Hz with a peak over the 9–12 Hz band (Figure 4). Prazosin induced highly significant increases in power from 5 Hz whereas phenoxybenzamine had only a slight effect on components 3–5 Hz (Figure 4). The EEG spectra of modafinil and prazosin were the inverse of each other (Figure 5).

The changes of EEG spectral power related to the decrease of noradrenergic transmission by UK 14304 and clonidine are shown in Figure 4C,D, respectively. They were characterized by a significant increase in nearly all the frequency range from 1–30 Hz, with a peak at 13 Hz. Clonidine (0.025 mg kg^{-1}) increased the power of EEG spectra not only at fast frequencies but also in slow frequency components. UK 14304 (0.05 mg kg^{-1}) did not increase the power over 1–3 Hz significantly. The second difference between the two drugs concerned the extent of increased power over the 14–24 Hz range which was more obvious after clonidine. The EEG spectra evoked by clonidine, UK 14304 and prazosin demonstrated dose-dependent relationships between dose and EEG power (Figure 6).

Prazosin interactions

When cirazoline (0.64, 1.25 and 2.5 mg kg^{-1} s.c.) or modafinil (250 and 350 mg kg^{-1} i.p.) were co-administered with prazosin (0.64 mg kg^{-1} s.c.) (Figures 7 and 8), this resulted in a significant dose-dependent attenuation of EEG changes induced by prazosin alone. In contrast, co-administration of apomorphine (0.01, 0.1 and 0.5 mg kg^{-1} s.c.) and prazosin (Figure 9) tended to enhance the prazosin-induced EEG effects. These opposite effects are clearly shown in Figure 10 where the averaged power changes from 8–10 Hz have been presented.

Discussion

The electroneurophysiological analysis of sleep has shown the importance of different ascending neurotransmitter systems. Thus, thalamic and cortical neuronal activities are under the control of cholinergic, serotoninergic, histaminergic, GABAergic and noradrenergic modulatory systems (Steriade *et al.*, 1993a,b). Noradrenaline released from locus coeruleus neurons acts in conjunction with acetylcholine released from the brainstem and basal forebrain during wakefulness (Steriade *et al.*, 1990b; 1993c). Neurophysiological evidence has confirmed that thalamic relay neurons display rhythmic bursts consisting of oscillation in the frequency range of 0.5–4 Hz and spindle

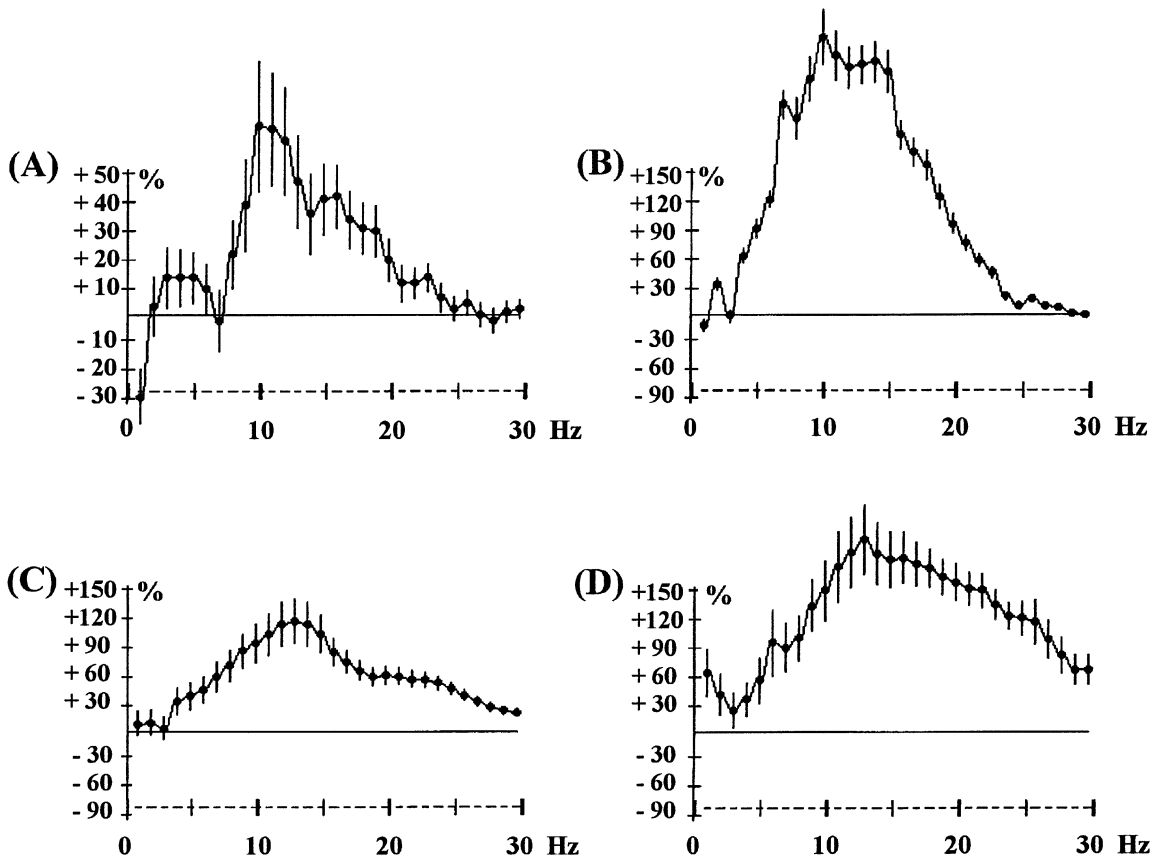

Figure 4 Effects of phenoxybenzamine, 0.64 mg kg^{-1} s.c. (A), prazosin, 0.32 mg kg^{-1} s.c. (B), UK 14304, 0.05 mg kg^{-1} s.c. (C) and clonidine, 0.025 mg kg^{-1} i.p. (D) expressed as per cent change of EEG spectral power in the prefrontal cortex of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals.

oscillations in the frequency range 7–14 Hz (Steriade *et al*., 1993c) during slow-wave sleep. Noradrenergic neurons of the locus coeruleus, conjointly with mesopontine cholinergic neurons (Steriade *et al*., 1990a; 1993b; McCormick, 1992), modulate thalamic neurons firing through a slow depolarization by blockade of a resting potassium conductance, shifting from burst firing with synchronized sleep to a tonic discharge pattern during wakefulness (Steriade *et al*., 1990b). Disruption of spindle oscillations, which are compatible with the notion of an ascending activating system, operate during EEG, desynchronized behavioural states of wakefulness (Steriade *et al*., 1990a). Activation of α_1-adrenoceptors can result in suppression of rhythmic burst firing in thalamic neurons and thalamocortical systems, with consequent depolarization of cortical neurons (McCormick, 1992; Steriade *et al*., 1993a,b), through the reduction of specialized potassium conductances (McCormick & Williamson, 1991). Stimulation of both cholinergic and noradrenergic neurons block the slow cortical oscillations (Steriade *et al*., 1993c).

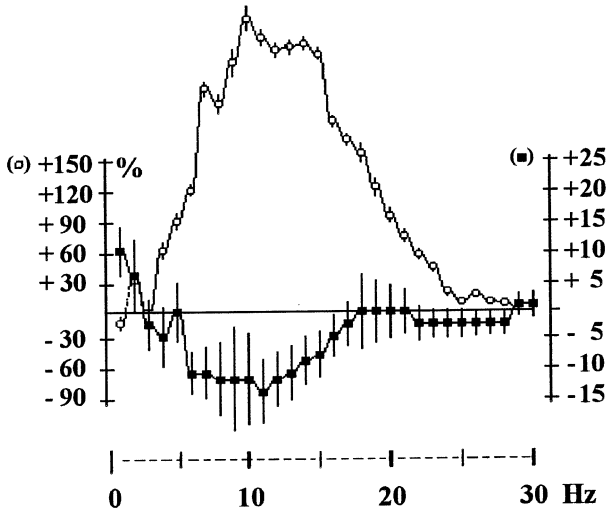

Figure 5 Simultaneous representation of prazosin (0.32 mg kg^{-1} s.c.) and modafinil (250 mg kg^{-1} i.p.) effects expressed as per cent change of EEG spectral power in the prefrontal cortex of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals.

Our studies have been conducted in conscious rats to evaluate if such relationships can be described in the awakened state. Transcortical bipolar electrodes were used to ascribe EEG changes to specific cortical regions and to allow spatially precise analysis of various pharmacological interventions. As described in Methods, the first exposed electrode was located on the cerebral cortex surface and the second exposed site was introduced through the cortex. Thus, the recorded EEG reflects only the local electrical events.

A great number of neuronal structures, with a non-tangential orientation relative to cortical surface must exhibit synchronous electrical phenomena to create an electrical potential difference of a few microvolts between the electrodes. This explains why the observation of rhythmic changes on EEG records is called synchronization and inversely, the disappearance of such rhythms is called desynchronization. For example, desynchronization classically occurs on opening the eyes when alpha activity is blocked. EEG traces depict energy variations versus time whereas power spectra used in this study describe the energy repartition according to the frequency. Over short periods of time (1 or 2 min), there is very good correspondence between the appearance or disappearance of rhythmic activities on EEG records and the change in power on the central frequency on these rhythmic activities.

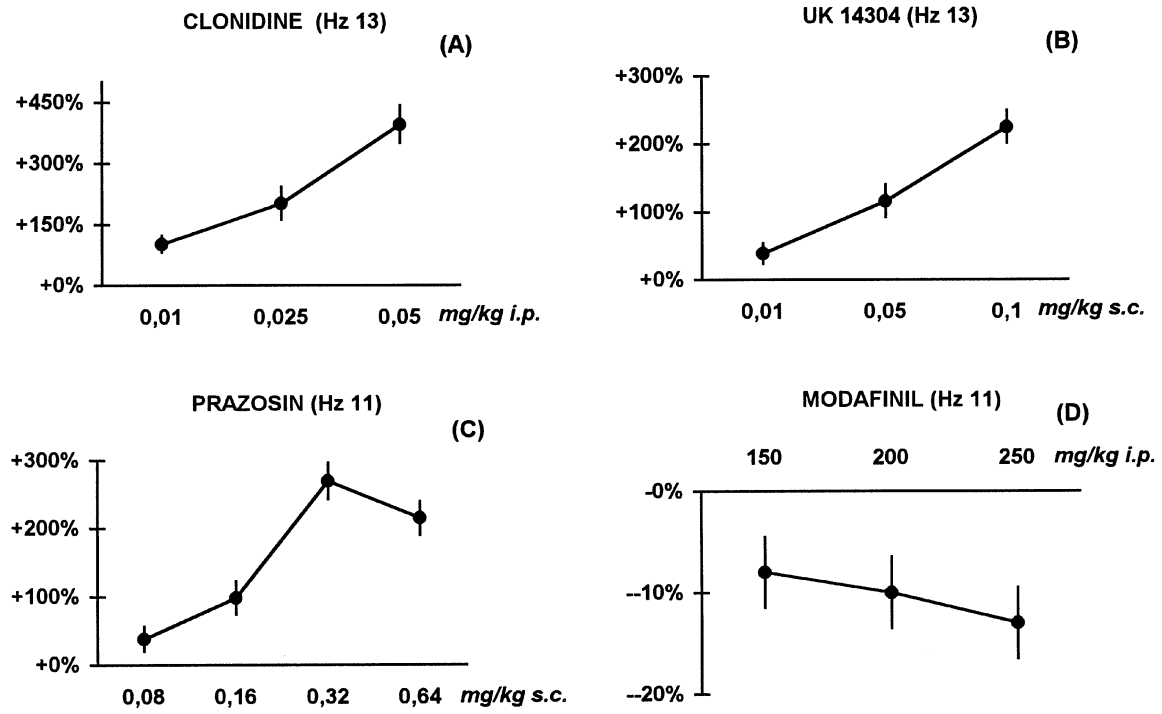

Figure 6 The relation between the changes of EEG spectral power in the prefrontal cortex and the doses of clonidine i.p. at 13 Hz (A), UK 14304, s.c., at 13 Hz (B), prazosin, s.c., at 11 Hz (C) and modafinil, i.p., at 11 Hz (D) in rats. The abscissa represents the dosage. The ordinate indicates the percentage change produced by drug administration. Vertical bars show 95% confidence intervals, calculated at each dose.

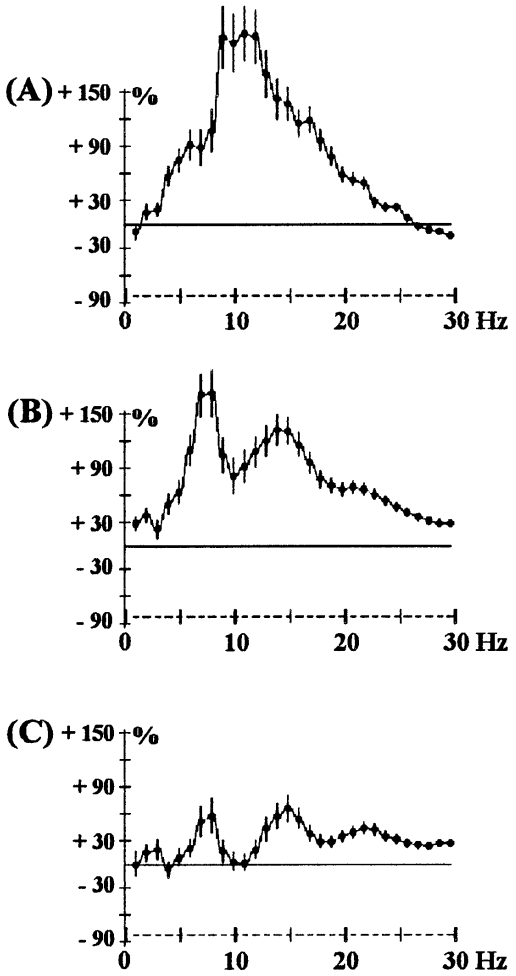

Figure 7 Effects of prazosin alone 0.64 mg kg^{-1} s.c. (A), co-administration of prazosin and modafinil 250 mg kg^{-1} i.p. (B) and co-administration of prazosin and modafinil 350 mg kg^{-1} i.p. (C) expressed as per cent change of EEG spectral power in the prefrontal cortex of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals.

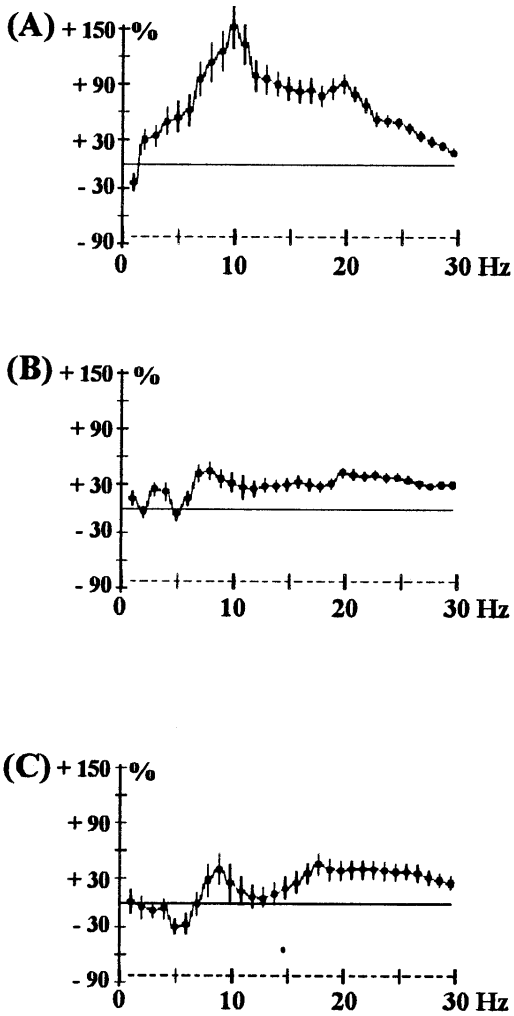

Figure 8 Effects of co-administration of prazosin 0.64 mg kg^{-1} s.c. and cirazoline 0.64 mg kg^{-1} s.c. (A), co-administration of prazosin and cirazoline 1.25 mg kg^{-1} s.c. (B) and co-administration of prazosin and cirazoline 2.5 mg kg^{-1} s.c. (C) expressed as per cent change of EEG spectral power in the prefrontal cortex of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals.

In many recent studies describing events related to desynchronization as well as less likely events related to synchronization, power changes calculated with fast Fourier transformation have been used by many authors (Derambure *et al*., 1993; Pfurtscheller, 1992; Pfurtscheller *et al*., 1997). Even if a closer correlation could be observed between synchronization on EEG recordings and the power distribution using wavelet analysis, it can be assumed that there is a strong relationship between EEG power calculated on one EEG signal epoch and synchronization or desynchronization observed during the same time. Thus, synchronization may be taken as an increase in the power spectra in our studies and desynchronization as a reduction.

Both apomorphine and quinpirole are dopaminergic agonists and increase sleep and decrease wakefulness when administered at a low dose (Creese *et al*., 1982; Monti *et al*., 1989). However, they induce the opposite effects at high doses. Thus, both drugs exerted biphasic effects on sleep and wakefulness (Gaillard, 1990) as well as behaviour (Eilam & Szechtman, 1989; Möller, 1987). The biphasic effects can also be seen from the changes of EEG spectral power observed in our experiments. Indeed, as a function of the dose, there were opposite changes in EEG spectral power. Both drugs at low doses decreased the EEG power at low frequency and increased power at high frequencies. This kind of change may be related to stimulation of presynaptic dopaminergic autoreceptors and thus to a decrease of dopamine release (Möller, 1987). Again, both drugs at high doses induced the opposite change on EEG spectral power, characterized by an increase in slow wave power (1–5 Hz), and a decrease of fast activities (6–30 Hz). One possible mechanism is that stimulation of post-synaptic receptors by high doses of these dopamine agonists increases arousal, thereby leading to EEG desynchronization.

The dopaminergic antagonists, raclopride and haloperidol, which decreased dopaminergic transmission by blocking dopaminergic D_2 and D_3 receptors, synchronized EEG activities and resulted in an increase of the EEG spectral power at the same frequencies as those modified by low doses of apomorphine or quinpirole.

In this study, we investigated the effects of α_1- and α_2-adrenoceptor agonists and antagonists on cortical electric activity in the prefrontal cortex of rats. The characteristics of EEG spectral power caused by drugs which increased noradrenergic transmission, as well as drugs which stimulate directly post-synaptic receptors, was decreased power in the frequency range 6–18 Hz with a maximum at 11 Hz. Yohimbine or RX 821002 each increase activity of locus

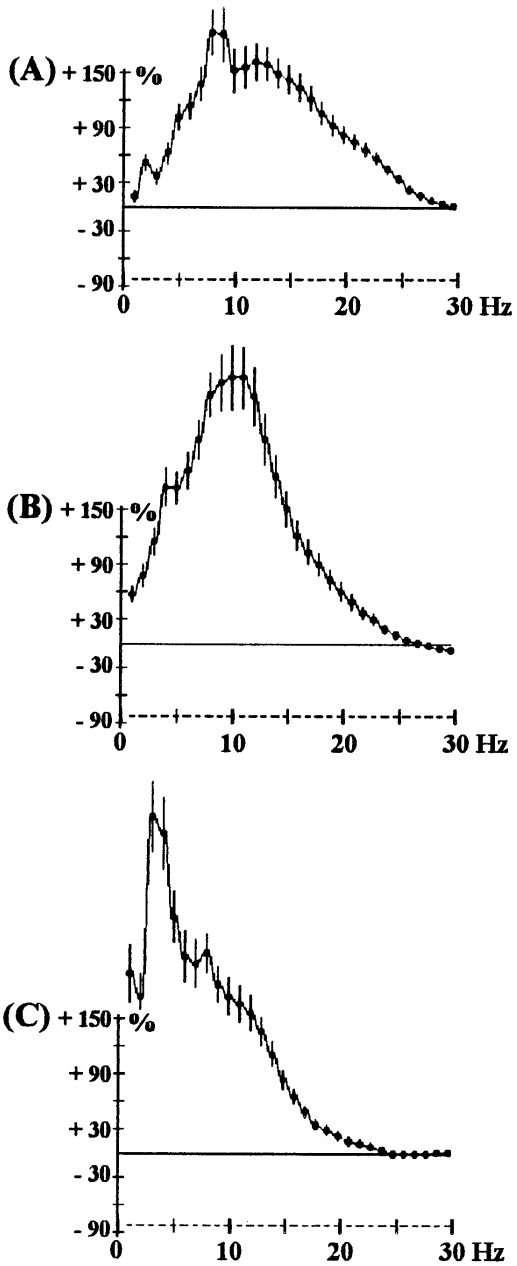

Figure 9 Effects of co-administration of prazosin 0.64 mg kg^{-1} s.c. and apomorphine 0.01 mg kg^{-1} s.c. (A), co-administration of prazosin and apomorphine 0.1 mg kg^{-1} s.c. (B) and co-administration of prazosin and apomorphine 0.5 mg kg^{-1} s.c. (C) expressed as per cent change of EEG spectral power in the prefrontal cortex of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals.

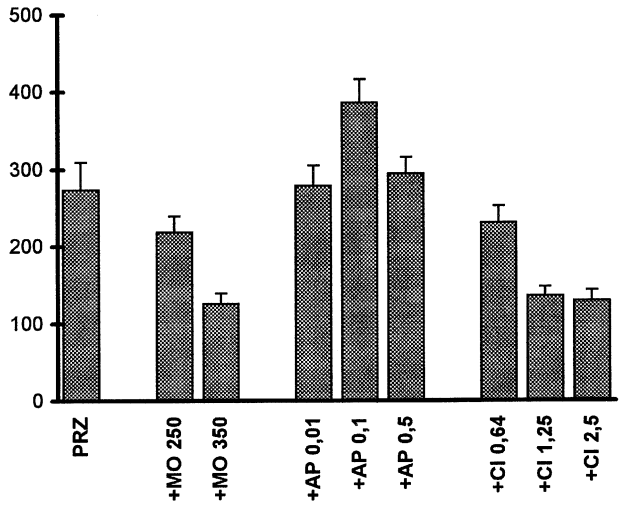

Figure 10 Averaged per cent EEG power changes and their 95% confidence interval for the 8–10 Hz frequences after prazosin alone (PRZ 0.64 mg kg^{-1} s.c.) and different coadministered drugs: modafinil (MO, 250 and 350 mg kg^{-1} i.p.), apomorphine (AP, 0.01, 0.1, 0.5 mg kg^{-1} s.c.) and cirazoline (CI, 0.64, 1.25, 2.5 mg kg^{-1}, s.c.).

coeruleus neurons (Timmermans *et al.*, 1981; Gobert *et al.*, 1998) by α_2-adrenoceptor antagonism. They can bring about similar EEG changes to α_1-adrenoceptor agonists as reflected in a decreased EEG power. These results are in accordance with those of Sarro *et al.* (1988). The EEG changes induced by modafinil were the opposite of those induced by prazosin and modafinil antagonized the effects of prazosin. The present data confirm the distinct pharmacology of modafinil, which despite being devoid of affinity for known α_1-adrenoceptors, mimics in some respects the effects of α_1-adrenoceptor agonists. Despite the marked effects on noradrenergic function, the compound has a very weak affinity for the dopamine transporter (Mignot *et al.*, 1994), and although the drug does not increase dopamine release in the striatum (De Séréville *et al.*, 1994), modafinil increases dopamine release from the nucleus accumbens (Ferraro *et al.*, 1996). Thus, despite having major effects in the noradrenergic system, a weak effect on dopaminergic systems cannot be ruled out.

The drugs decreasing noradrenergic transmission evoked similar changes of EEG spectral power, and were characterized by increased power over nearly all frequencies (1–30 Hz). The shape of EEG spectral power was different between the α_1-adrenoceptor antagonists and α_2-adrenoceptor agonists. These phenomena may be related to the different mechanism by which they mediate noradrenergic transmission. In comparison with phenoxybenzamine or prazosin, the peak increase in power of EEG spectra evoked by the α_2-adrenoceptor agonists, UK 14304 and clonidine, was maximum at 13 Hz. The presynaptic effects of α_2-adrenoceptor agonists (Kobinger, 1984; Aghajanian & Wang, 1987) result in inhibition of the rate of firing of central noradrenergic neurons (Aghajanian & Wang, 1987). The hyperpolarization of the locus coeruleus, by increasing potassium conductance (Funke *et al.*, 1993), may elicit an increased degree of EEG synchronization (Steriade & Contreras, 1995).

Although we explored the possible mechanism of changes of EEG spectral power produced by dopaminergic agonists and antagonists, α_1- and α_2-adrenoceptor agonists and antagonists respectively, it must be emphasized that global EEG activity reflects a variety of oscillations generated in the thalamus and cerebral cortex (Bradshaw *et al.*, 1983; Gaillard, 1990; Steriade *et al.*, 1993c). Furthermore, some neurons synthesize and release more than one transmitter and many interactions have been demonstrated between the noradrenergic and dopaminergic system (Gaillard, 1990; Gobert *et al.*, 1998). Consequently, the precise changes in EEG following the administration of noradrenergic, dopaminergic agonists and antagonists are complex to interpret. When agonists and antagonists of the same receptor type were co-administered, a dose-dependent EEG interaction can be described. This was the case for the co-administration of prazosin and cirazoline. The integrative value of EEG analysis was underlined by the observation of a dose-dependent interaction between prazosin and modafinil, a drug without significant binding to α_1-adrenoceptors, but where the behavioural effects were dose-

dependently antagonized by prazosin. Again, the complex pattern of EEG interactions observed when apomorphine and prazosin were co-administered agree with the results published by Tassin *et al*. (1992) using unitary extracellular recording.

Nevertheless, comparing the drug-induced changes of EEG spectral power, we conclude that a decrease of dopaminergic or noradrenergic transmission induces an increase of EEG spectral power. Drugs modulating central neurotransmitters by different mechanisms have substantially different EEG power spectra, despite generating apparently similar pharmacological effects. Thus, analysis of EEG spectral power in conscious rats may provide a link to the definition of a pharmacological profile, which we are correlating with clinical studies on EEG.

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