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Effects of phencyclidine (PCP) and MK 801 on the EEGq in the prefrontal cortex of conscious rats; antagonism by clozapine, and antagonists of AMPA-, α_1- and 5-HT_{2A}-receptors

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1 The electroencephalographic (EEG) effects of the propsychotic agent phencyclidine (PCP), were studied in conscious rats using power spectra (0–30 Hz), from the prefrontal cortex or sensorimotor cortex. PCP (0.1–3 mg kg^{-1} s.c.) caused a marked dose-dependent increase in EEG power in the frontal cortex at 1–3 Hz with decreases in power at higher frequencies (9–30 Hz). At high doses (3 mg kg^{-1} s.c.) the entire spectrum shifted to more positive values, indicating an increase in cortical synchronization. MK 801 (0.05–0.1 mg kg^{-1} i.p.) caused similar effects but with lesser changes in power.

2 In contrast, the non-competitive AMPA antagonists GYKI 52466 and GYKI 53655 increased EEG power over the whole power spectrum (1–10 mg kg^{-1} i.p.). The atypical antipsychotic clozapine (0.2 mg kg^{-1} s.c.) synchronized the EEG (peak 8 Hz). The 5-HT_{2A}-antagonist, M100907, specifically increased EEG power at 2–3 Hz at low doses (10 and 50 μg kg^{-1} s.c.), whereas at higher doses (0.1 mg kg^{-1} s.c.) the profile resembled that of clozapine.

3 Clozapine (0.2 mg kg^{-1} s.c.), GYKI 53655 (5 mg kg^{-1} i.p.), prazosin (0.05 and 0.1 mg kg^{-1} i.p.), and M100907 (0.01 and 0.05 mg kg^{-1} s.c.) antagonized the decrease in power between 5 and 30 Hz caused by PCP (1 mg kg^{-1} s.c.), but not the increase in power at 1–3 Hz in prefrontal cortex. *British Journal of Pharmacology* (2002) **135,** 65–78

Keywords: Prefrontal cortex; phencyclidine (PCP); clozapine; AMPA; GYKI 52466; 5-HT_{2A}-receptors; M100907; EEG; schizophrenia

Abbreviations: AMPA, alpha-3-amino-hydroxy-5-methyl-4-isoxazole propionic acid; DMT, dimethyltryptamine; EEG, electroencephalogram; 5-HT, 5-hydroxytryptamine; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine

Introduction

The prefrontal cortex is crucial for coordination of working memory and attention in man and rodents (Ungerleider, 1995; Posner, 1997; Wharton & Grafman, 1998). Numerous observations suggest that its innervation may be compromised in schizophrenia. Blood flow in the prefrontal cortex is modified in schizophrenia (Weinberger *et al*., 1986; Weinberger, 1987; 1996) and, recently, an abnormal activation of the dorsolateral prefrontal cortex, through its projections from the mediodorsal nucleus of the thalamus, has been claimed to be causative in schizophrenia (Manoach *et al*., 2000; Bunney & Bunney, 2000). Bunney & Bunney (2000) have also speculated that changes in NMDA receptor composition during development of the prefrontal cortex could be causative. Abnormalities in the neural circuits in the prefrontal cortex, which are involved in working memory, are the basis of the model of schizophrenia proposed by Goldman-Rakic (1991), Goldman-Rakic *et al*. (2000), and have been shown in imaging studies (Crespo-Facorro *et al*., 2000). A robust reduction (<3.5 million) in the number of thalamic neurones innervating frontal regions has been reported in schizophrenics (Young *et al*., 2000). Thus the prefrontal cortex is a key area for the investigation of antipsychotic drugs.

Phencyclidine (PCP) is an *N*-methyl-D-aspartate (NMDA) antagonist which induces hallucinations in man. PCP, and its less active congener, ketamine, have been shown to exacerbate existing psychotic disorders in schizophrenics and to reactivate symptoms in remittance (Luby *et al*., 1959; Cohen *et al*., 1962; Allen & Young, 1978; Ellison, 1995; Lahti *et al*., 1995; Malhotra *et al*., 1997a, b; reviewed in Jentsch & Roth, 1999). The abnormal startle response in schizophrenia (Braff *et al*., 1992) is mimicked by administration of PCP (Geyer *et al*., 1984) The chronic effects of low doses of PCP on social behaviour in primates have been proposed as a model for schizophrenia (Frederick *et al*., 1995; Jentsch *et al*., 1997b). Detailed analysis of the cognitive changes induced by low doses of ketamine in volunteers have shown direct similarities with the cognitive changes induced by schizophrenia (Malhotra *et al*., 1996b; 1997a); the same has been shown by PCP (Goldman-Rakic, 1991). Thus there is strong evidence that the NMDA antagonists PCP, ketamine, and MK801 may be used to model schizophrenia (Abi-Saab *et al*., 1998).

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PCP and other NMDA antagonists increase glutamate release in the prefrontal cortex; glutamate release may modulate other transmitter systems, including dopamine (Takahat & Mogaddam, 1998). Classically, D_2-receptor antagonism is considered to be a core aspect of antipsychotic action, yet effects of PCP on working memory, used to model frontal lobe deficits, and hyperlocomotion, used to model psychosis, may be distinguished from the activator effects on dopaminergic transmission (Adams & Moghaddam, 1998). Furthermore, the propsychotic effects of ketamine in man are resistant to the D_2 antagonist, haloperidol, in comparison with clozapine (Malhotra *et al*., 1997a,b; Krystal *et al*., 1999). PCP induces impairments in spatial memory in rodents, similar to those seen in schizophrenia, and these changes are inhibited by antipsychotic agents (Verma & Moghaddam, 1996), but the effects of PCP on dopamine are insufficient to account for the induced symptoms the glutamatergic hyperstimulation is responsible (Adama & Mogaddam, 1998). The effects of PCP on the startle response are antagonized by clozapine (Bakshi *et al*., 1994; Bakshi & Geyer, 1995) and olanzepine (Bakshi & Geyer, 1995). The locomotor effects of PCP have been shown to be specifically blocked by the atypical antipsychotics clozapine and S16924, at >100 fold lower doses than those required to block the locomotor effects of the dopaminergic agonists, amphetamine and apomorphine (Millan *et al*., 1998); in contrast haloperidol was equieffective against PCP and amphetamine. Furthermore the locomotor effects of PCP *in vivo* and *in vitro* were blocked by low doses of the 5-HT_{2A} antagonist M100907 (Maurel-Remy *et al*., 1995; Wang & Liang, 1998), which suggests a role for 5-HT_{2A} receptors in the effects of PCP.

5-HT_{2A} receptors may play a pivotal role in schizophrenia (Bennett *et al*., 1979; Burnet & Harrison, 1996). A study of the abnormalities in 5-HT_{2A} receptor mRNA from frontal cortex of chronic elderly schizophrenics, either treated with neuroleptics at the time of death, or drug-free for at least six months, showed decreased expression of mRNA for the receptor which was restored by drug treatment (Dean & Hayes, 1996; Dean *et al*., 1996; Hernandez & Sokolov, 2000). Genetic analysis (although not necessarily sequence analysis) has associated a polymorphism of the 5-HT_{2A} receptor gene with schizophrenia (102−T/C; Erdmann *et al*., 1996; Inayama *et al*., 1996). This polymorphism has been associated with a beneficial response to clozapine (Arranz *et al*., 1996; 1998). Similar polymorphisms have been associated with an increased risk of suicide.

The present paper describes these interactions in the EEG of the prefrontal cortex of conscious rats (Sebban *et al*., 1999a, b) following exposure to substances acting on NMDA, AMPA, 5-HT2A receptors and a1-adrenoceptors. We have characterized more than 50 drug-induced changes in the present model of EEG of prefrontal cortex, using the somatosensorimotor region as a control for effects on motor functions (Sebban *et al*., 1987; 1999a, b). Chronically implanted EEG leads in the prefrontal cortex of conscious rats are used to obtain 'finger prints' of drug profiles over the

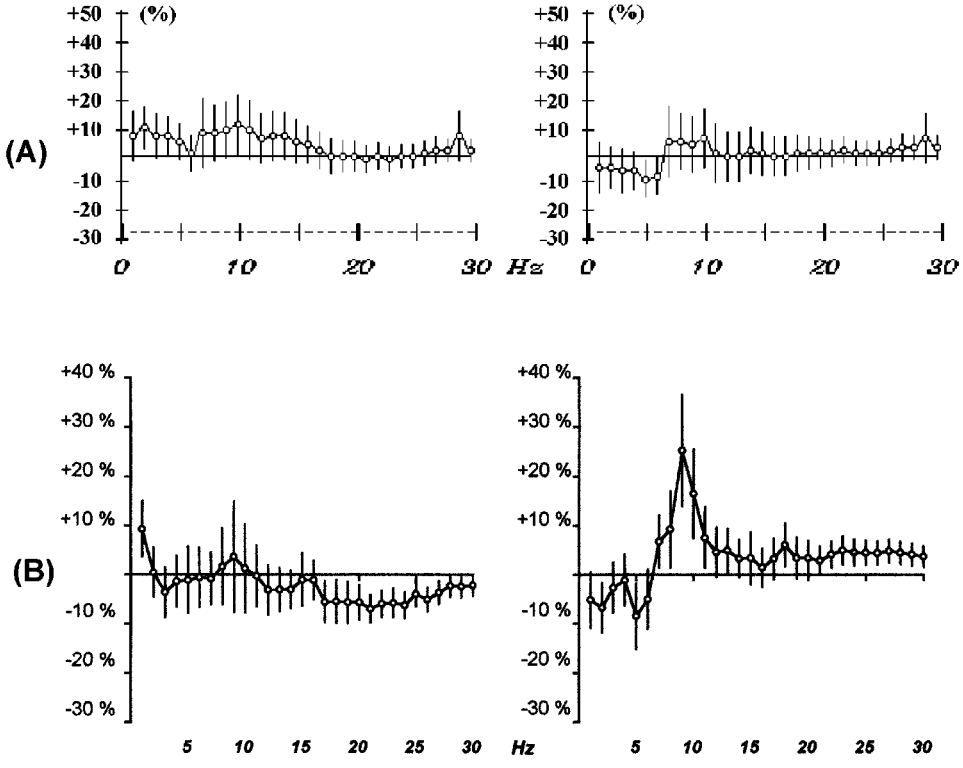

Figure 1 Effects of injection of saline (0.1 mg kg^{-1}, i.p.; A) or acid vehicle (0.01 M HCl; B) on EEG spectral power in the prefrontal cortex (left panels) and sensorimotor cortex (right panels) in conscious rats. The abscissa represents the EEG spectral component between 1 and 30 Hz. The horizontal 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 saline administration 24 h earlier. Vertical bars for each Hz show 95% confidence intervals ($n=6$).

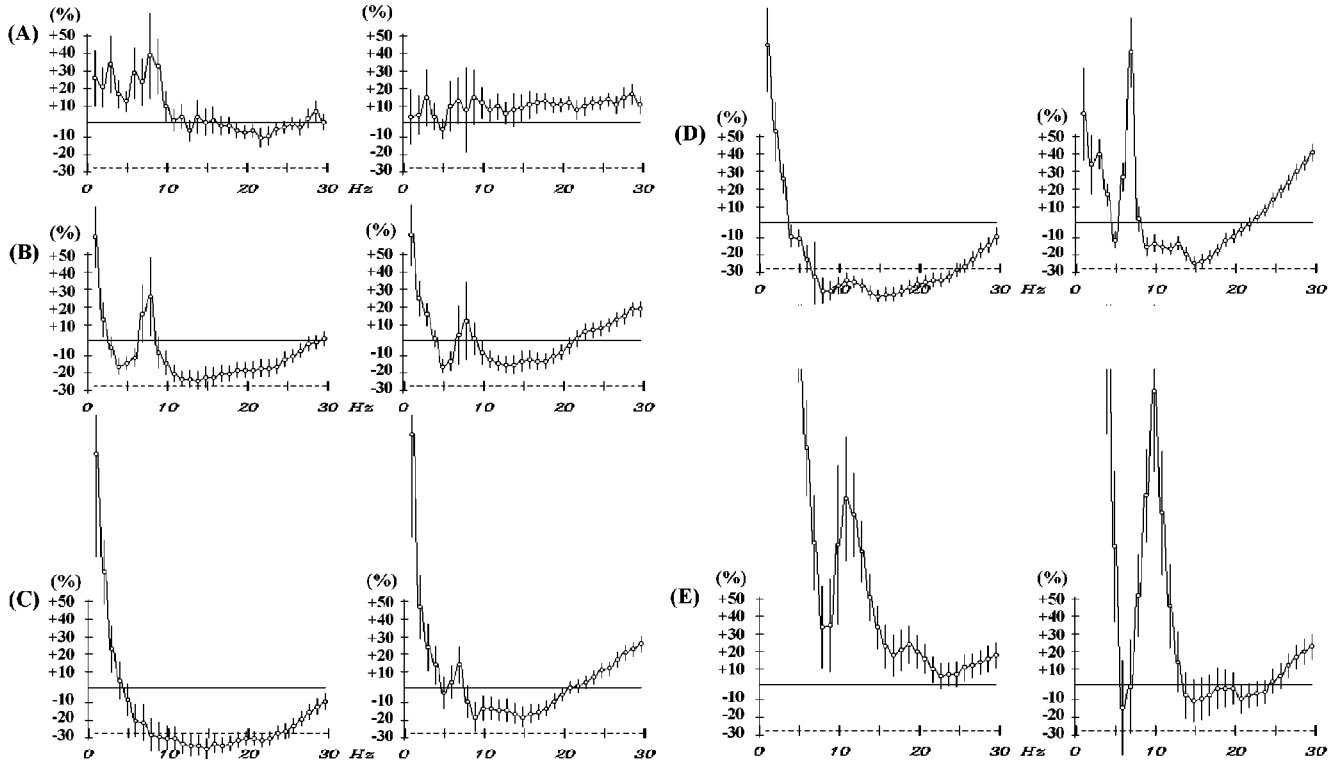

Figure 2 Dose-reponse effects of phencyclidine (PCP) on EEG spectral power in the prefrontal cortex (left panels) and sensorimotor cortex (right panels) in conscious rats. The abscissa represents the EEG spectral component between 1 and 30 Hz. The horizontal line at zero indicates no change. The ordinate 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 ($n=6$). A: 0.1 mg kg^{-1} s.c.; B: 0.5 mg kg^{-1} s.c.; C: 1 mg kg^{-1} s.c.; D: 1.25 mg kg^{-1} s.c.; E: 3 mg kg^{-1} s.c.

range of 1–30 Hz (Sebban *et al*., 1999a, b). We have reported that activation of noradrenergic and dopaminergic receptors causes a decrease in EEG power (desynchronization) whereas inhibition of these two systems increases EEG power (synchronization) (Sebban *et al*., 1999a, b). Decreases in EEG power in this model are induced by agents which increase vigilance, such as modafinil (Sebban *et al*., 1999a, b). In comparison, other electrophysiological studies have shown that delta waves and spindle activity are inhibited by stimulating noradrenergic neurones and cholinergic nuclei in animals (Steriade *et al*., 1990a; 1991; 1993a, b, c). Theta rhythm (~8 Hz) in the prefrontal cortex is increased by a wide range of antipsychotic drugs (clozapine, haloperidol, chlorpromazine, risperidone, sertraline) (Sebban *et al*., 1999a, b). Drugs claimed to be cognition enhancers (piracetam, donepezil, Kinney *et al*., 1999) increase theta rhythm in urethane-anaesthetized rats, whereas NMDA antagonists such as dizolcipine decrease it. AMPA, injected into the septum in urethane-anaesthetized rats, increases theta rhythm, an effect which is antagonized by AMPA antagonists (Puma & Bizot, 1999). Furthermore muscarinic agonists injected into the septum also increase theta rhythm, but by a GABAergic mechanism (Shanabrough *et al*., 2000). Thus direct modulation of the EEG may reflect cognitive processes.

The effects of PCP on EEG have been evaluated by Mattia & Moreton (1986) and Yamamoto (1997), but with very different results. In the first study using rats and restricted to an evaluation of EEG changes for 1–10 Hz frequencies, PCP 2 mg kg^{-1} i.p. injection was followed by an increase in the power of 6–8 Hz, accompanied by behavioural arousal and hyperactivity. Higher dosages (4 and 8 mg kg^{-1} i.p.) induced an important increase in delta power (1–3 Hz) with limited locomotion, ataxia and stereotypy. After 0.5 mg kg^{-1} i.p. PCP, Yamamoto (1997) observed modest reductions in EEG power in cerebral cortex of the rabbit with an increase in hippocampal theta rhythm. Hippocampal γ waves may be increased by PCP (Ma & Leung, 2000).

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±2°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 (Sebban *et al*., 1999a, b). Four trans-cortical bipolar electrodes were thus inserted. Each electrode had one exposed

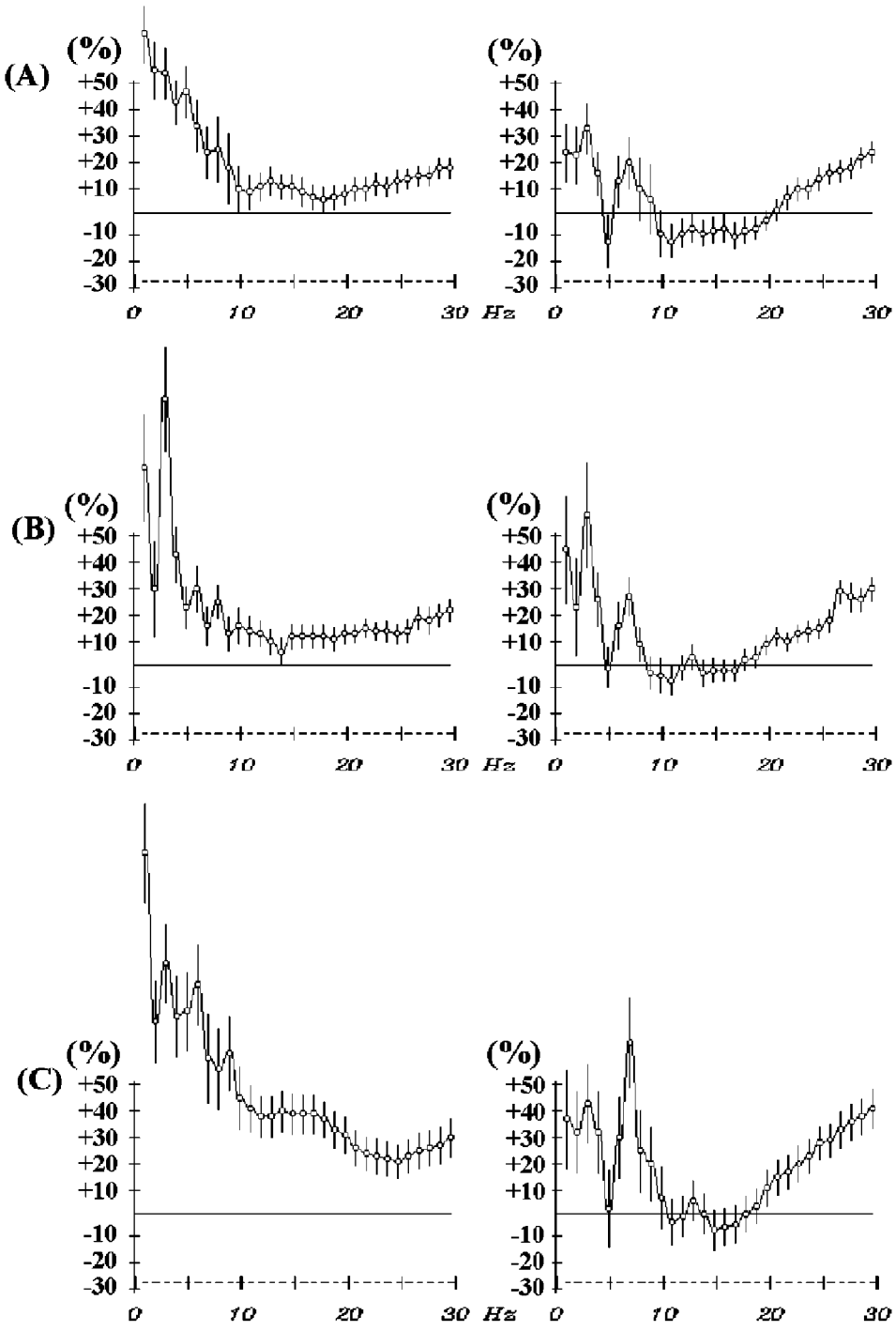

Figure 3 Effects of MK 801 (dizolcipine, 0.05 (A), 0.075 (B), 0.1 (C) mg kg^{-1} i.p.) on EEG spectral power in the prefrontal cortex (left panels) and sensorimotor cortex (right panels) in conscious rats. The abscissa represents the EEG spectral component between 1 and 30 Hz. The horizontal line at 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 ($n=6$).

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.

Ten 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

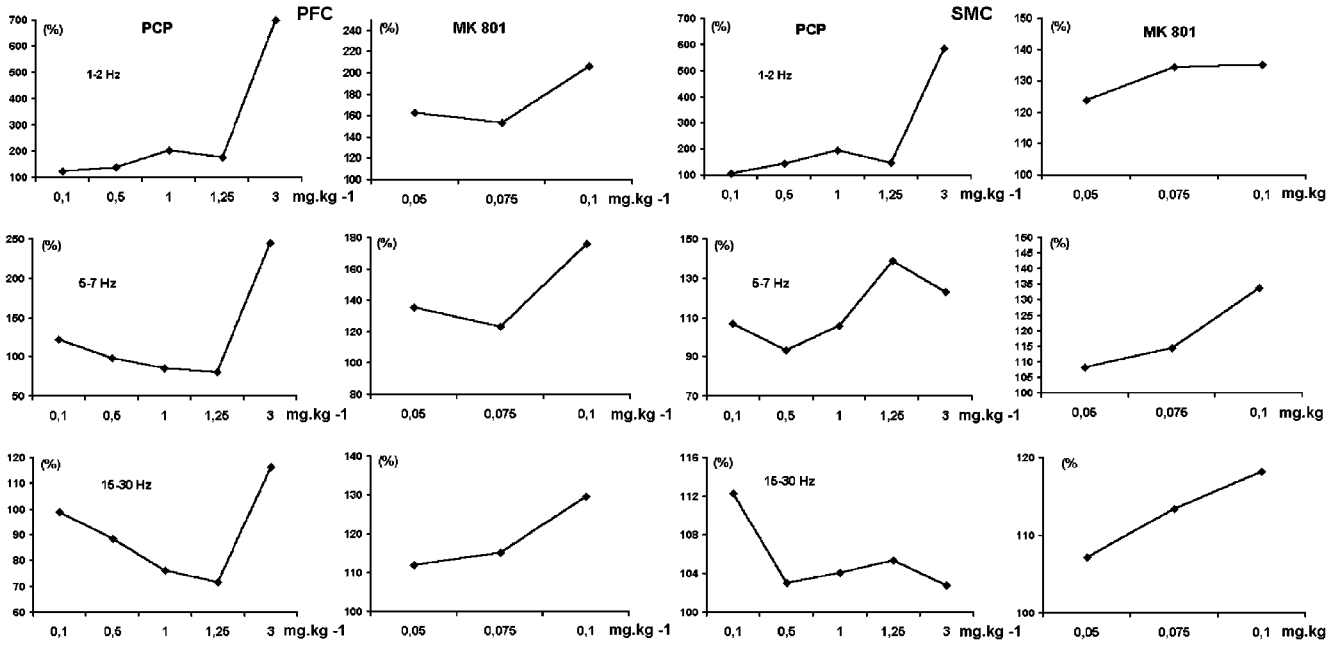

Figure 4 Dose-response relationship for PCP and MK 801 on EEG spectral power in the prefrontal cortex (PFC) and sensorimotor cortex (SMC) in conscious rats. The abscissa represents the per cent change in the EEG power spectrum produced by drug administration, averaged over the frequency bands indicated (1–2 Hz; 5–7 Hz; 15–30 Hz). 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.

decrease artefacts of movement. It needed about 10–14 days for the rats to adapt to EEG recording.

EEG recording

The EEG changes induced by one single drug have been evaluated using the methodology described by Sebban *et al*., 1999a, b. When more than one dose has been evaluated, the order of doses was randomly chosen for each rat. Also, a one week drug-free interval was imposed between the study of two different doses of the same drug. For each dose, two EEG recordings were performed in each rat. The first recording lasted for 165 min after i.p. or s.c. injection of vehicle. The second was done 24 h later for the same duration following drug administration. As indicated below, these two records allow the evaluation of the treatment effect relative to the vehicle in one animal, by subtracting the effect of the vehicle. Nevertheless to have a better appreciation of any effect of the vehicle, some experiments have been performed with vehicle administration at D0 and D1; at D0, animals were injected with saline and at day 1 with saline, or with 0.01 M HCl (Figure 1).

The recordings were obtained at the same time every day to avoid the bias caused by nycthemeral EEG variations. EEG recordings were performed by placing the rat in a restraining cage 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 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 changes 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: GYKI 52466, GYKI 53655 (gifts from Dr A Egyed, EGIS), phencyclidine (PCP; Sigma), clozapine (Sigma), MK 801 (Sigma), haloperidol (Sigma), prazosin (Sigma); M100907 was synthesised by Dr G Lavielle, IdRS. All drugs were dissolved in the minimum of HCl (0.01 M) and made up to volume with saline.

Data analysis

The EEG spectral power from the prefrontal and sensorimotor cortices in the left and right hemispheres were each averaged for every 5 min period for each 165 min recording session. 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:

$$\text{variation of mean spectral power } (\%) = \frac{\text{EEG power following drug}}{\text{EEG power following vehicle}} \times 100 \quad (1)$$

This procedure therefore allows for the change in EEG power, at each frequency, expressed as percent of the original power, induced by a drug, compared with the control, in the

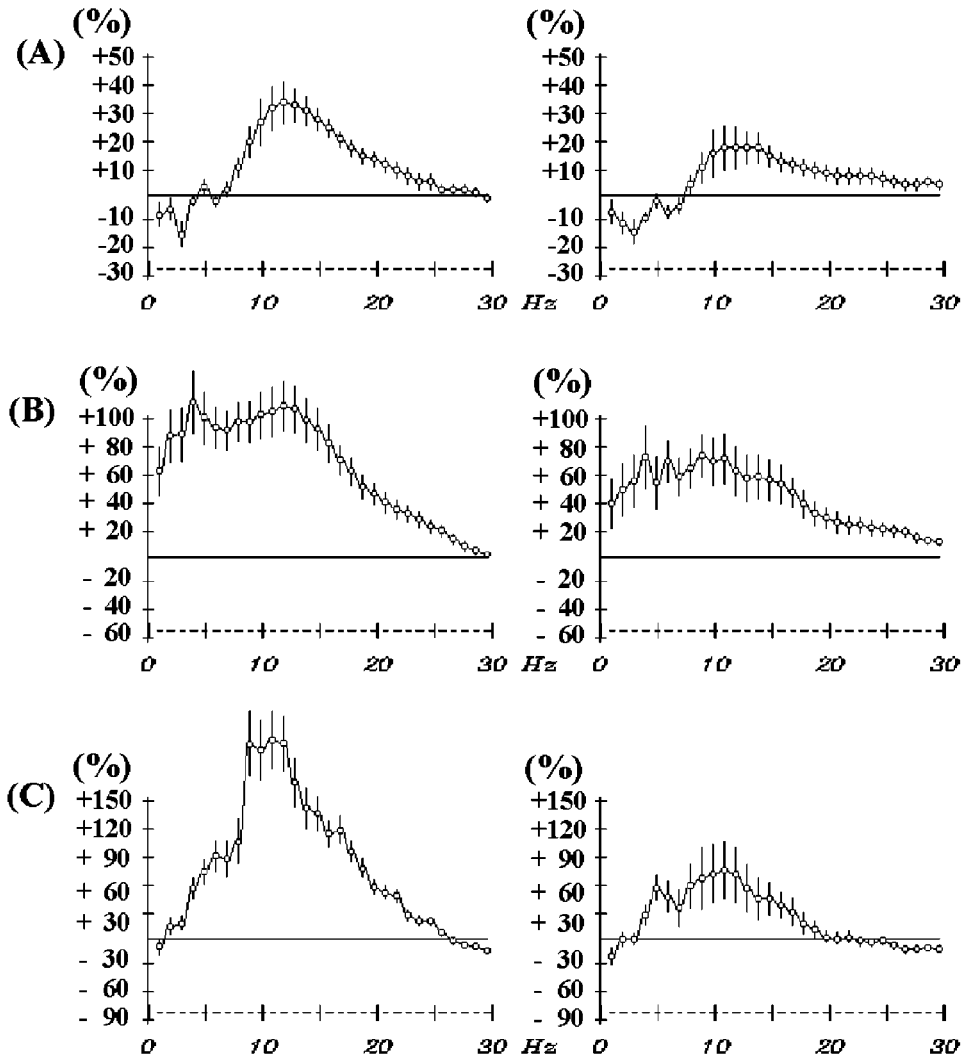

Figure 5 Comparison of the effects of haloperidol (0.5 mg kg^{-1} s.c., A), clozapine (0.2 mg kg^{-1} s.c., B), prazosin (0.64 mg kg^{-1} s.c., C) expressed as per cent change of EEG spectral power in the prefrontal cortex (left panels) and sensorimotor cortex (right panels) of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals, $n=6$). The ordinate indicates the percentage change produced by drug administration. Vertical bars show 95% confidence intervals, calculated at each dose.

same animal. This ratio was calculated at each 5 min interval after the beginning of recordings for 165 min.

The interactions between two drugs on the EEG were calculated as the ratio of mean spectral power obtained following the injection of both drugs versus the mean spectral power obtained following the administration of PCP, 1 mg kg^{-1} s.c.

$$\text{Attenuation of PCP} = 1 - \frac{\text{EEG power following the co-administration PCP + 2nd drug}}{\text{EEG power following PCP}} \quad (2)$$

With this formula, the characteristic of an attenuation identical at each frequency will be a horizontal line, parallel to the frequency axis. Full antagonism will appear on the graphics as a straight line parallel to the x axis; and crossing the y axis at the value 1, with enhancement yielding values less than 1 and an inversion of the effect yielding values greater than unity. Since EEG changes induced by PCP alone and by the co-administration of PCP and other compounds have not been evaluated on the same rats, attenuation curves could only be calculated on the average power changes observed on groups of six rats; the confidence intervals could not be estimated without making unjustified hypotheses.

Statistical analysis

For each dose of a 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 (1st, 2nd and 3rd hour with 12 repetitions) and animals. The mean power change for each cortical region was calculated from the number of rats and the time. In this study, mean power changes have been calculated for the total recording duration (165 min). 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

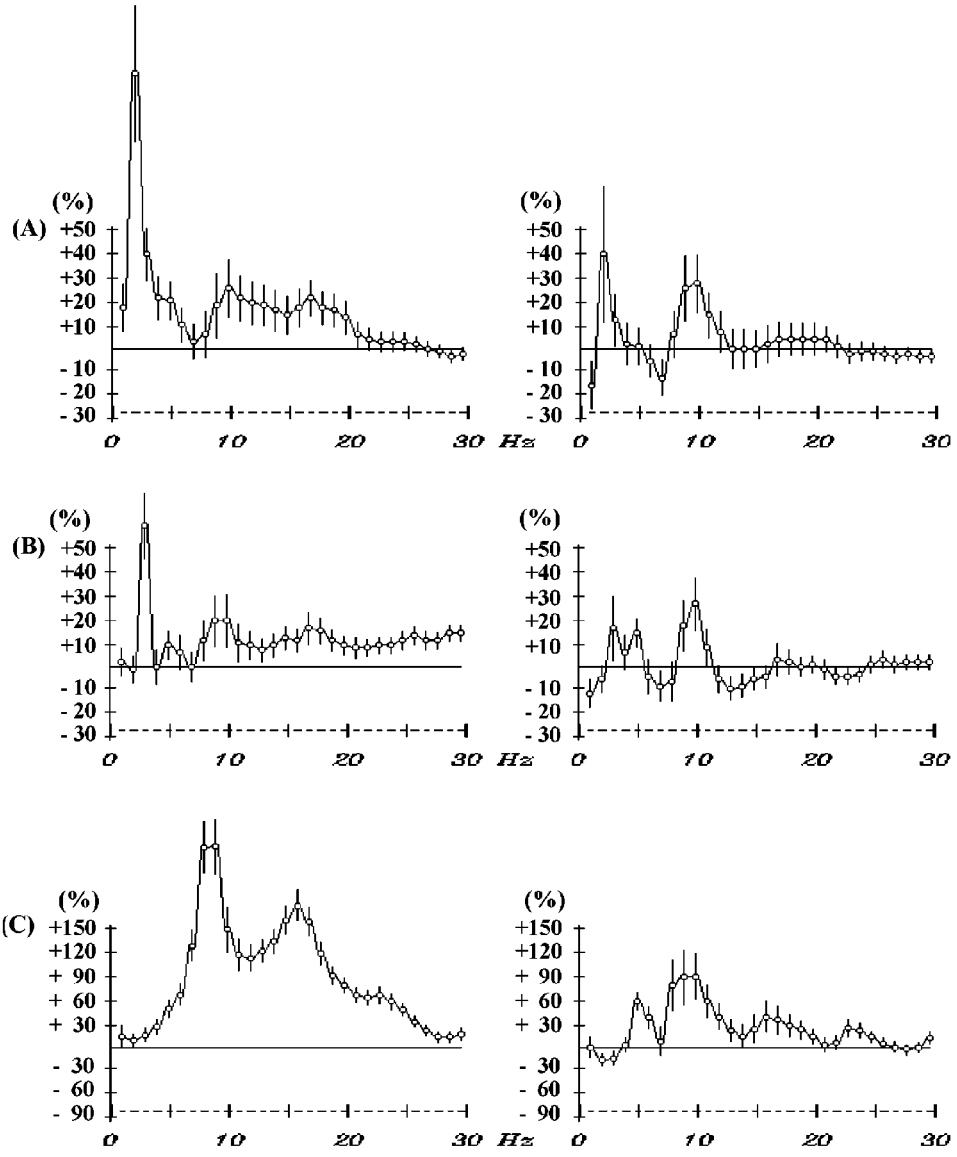

Figure 6 Dose-response relationship for M100907 (0.01 (A), 0.05 (B) 0.1 (C) mg kg^{-1} s.c.) expressed as per cent change of EEG spectral power in the prefrontal cortex (left panels) and sensorimotor cortex (right panels) of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals, $n=6$).

an increase or decrease in power, was taken as being significant.

Results

EEG variations observed between two successive days

When the same vehicle (physiological saline) was administered on two successive days, the EEG changes evaluated by the power ratios (day 1/day 0) showed that, whatever the examined frequency, the mean power variation was less than 10 % and did not reach a significant level (Figure 1). When physiological saline was administered at day 0 and the maximal amount of HCl used in any study was administered on day 1 (Figure 1), no significant EEG changes was observed in frontal cortex, while a slight, but significant increase of 8–10 Hz power was present in the sensorimotor cortex.

Effects of phencyclidine and MK 801

Phencyclidine, (PCP, 0.1–3 mg kg^{-1} s.c.), induced complex EEG changes according to frequency, cortical region and dose (Figure 2). In both cortices power was increased by up to 5 fold at very low frequencies (<4 Hz). A power decrement was observed at higher frequencies in prefrontal cortex, while EEG changes induced in sensorimotor cortex were mainly characterized by an increase in 7–8 Hz power and an increase in power for the 20–30 Hz band. At 3 mg kg^{-1} s.c. the entire power spectrum shifted to higher values, which further increased at 10 mg kg^{-1} s.c. (not shown).

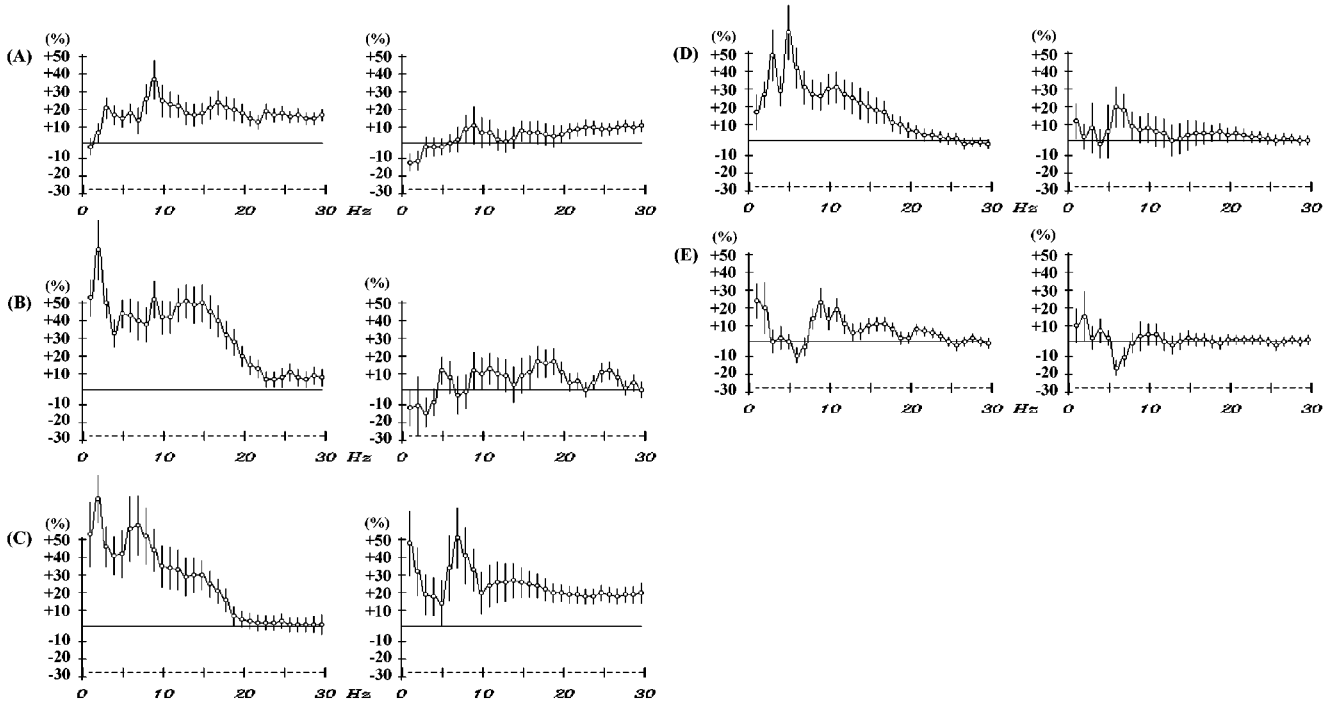

Figure 7 Effects of GYKI 52466 (1 (A), 5 (B) and 10 (C) mg kg^{-1} i.p.) and GYKI 53655 (1 (D) and 5 (E) mg kg^{-1} i.p.) expressed as per cent change of EEG spectral power in the prefrontal cortex (left columns) and sensorimotor cortex (right columns) of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals, $n=6$). Note the small selectivity window for prefrontal cortex for GYKI 52466.

The effects of MK 801 (0.05–0.1 mg kg^{-1} s.c., Figure 3) resembled those of PCP but without any significant decrease in EEG power. Despite this fact, some similarities were evident in the EEG changes produced by both drugs. For both drugs, significant dose-dependency was observed for their EEG effects. However, the dose-effect relationships were generally complex, and frequently U-shaped, as illustrated by Figure 4.

Effects of antipsychotics, AMPA antagonists, prazosin and M100907

In contrast (Figure 5), haloperidol (0.5 mg kg^{-1} i.p.), the atypical antipsychotic clozapine (0.2 mg kg^{-1} s.c.), and the α_1-adrenoceptor antagonist prazosin (0.64 mg kg^{-1} i.p.), all induced an increase in EEG power which was maximum for a middle frequency band (8–15 Hz), even if, as it is the case for clozapine, this power increase was also spread over lower frequencies. On the other hand (Figure 6), the selective 5-HT_{2A}-antagonist, M100907 (0.01 and 0.05 mg kg^{-1} s.c.) specifically increased EEG power at 2–3 Hz in prefrontal cortex. Higher doses (0.1 mg kg^{-1} s.c.) resulted in a profile similar to that of clozapine.

The non-competitive AMPA antagonists GYKI 52466 (1, 5 and 10 mg kg^{-1} i.p.) and GYKI 53655 (1 and 5 mg kg^{-1} i.p.) increased EEG power with maxima of 3 and 5 Hz, and slightly from 6 to 20 Hz (Figure 7). The effects of GYKI 52466 were most marked at low doses in the prefrontal cortex, with effects on sensorimotor cortex becoming more apparent at the higher doses, which are associated with the onset of ataxia. In contrast, the effects of GYKI 53655 on EEG were less marked at 5 mg kg^{-1} i.p.

Interactions with PCP

In the prefrontal cortex, clozapine (0.1, 0.2 and 0.3 mg kg^{-1} s.c.), haloperidol (0.5 mg kg^{-1} i.p.), GYKI 53655 (5 mg kg^{-1} i.p.) (Figure 8) as well as M100907 (0.01 and 0.05 mg kg^{-1} s.c.) and prazosin (0.05 and 0.1 mg kg^{-1} i.p.) (Figure 9), all inhibited the decrease in power between 5 and 30 Hz caused by PCP (1 mg kg^{-1} s.c.). Only the co-administration of GYKI 53655 (5 mg kg^{-1} i.p.) resulted in a significant reduction of the increase in very low frequency power induced by PCP. In graphs quantifying these interactions (Figure 10), clozapine, 0.2 mg kg^{-1}, caused the most complete inhibition of the effects of PCP in the prefrontal cortex.

Discussion

Transcortical bipolar electrodes allow a better degree of localization of the EEG effects of drugs in the awake state than do monopolar recordings. As described in the 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. The appearance of rhythmic activity on EEG records presumably represents synchronization of electrical events (EPSP and IPSP) on large populations of cortical vertical dendrites and inversely, the disappearance of such rhythms the desynchronization or reduced number of these electrical events. EEG traces depict energy variations *versus* time, whereas the power spectra used in this study

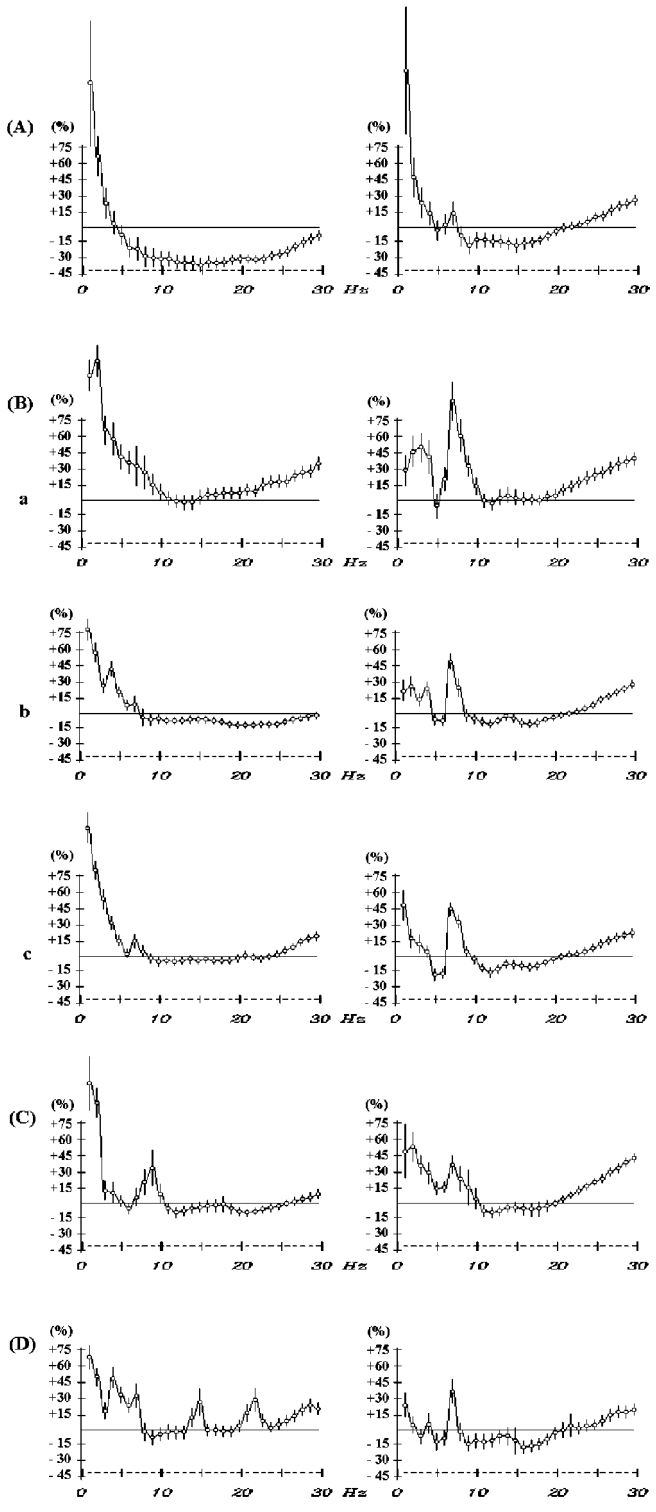

Figure 8 Administration of PCP alone (1 mg kg^{-1} s.c.) (A) and co-administration of PCP (1 mg kg^{-1} s.c.) and clozapine (B) (0.1 (a), 0.2 (b) and 0.3 (c) mg kg^{-1} s.c.), PCP (1 mg kg^{-1} s.c.) and haloperidol (C) (0.5 mg kg^{-1} i.p.), and PCP (1 mg kg^{-1} s.c.) and GYKI 53655 (D) (5 mg kg^{-1} i.p.) expressed as per cent change of EEG spectral power in the prefrontal cortex (on the left) and sensorimotor cortex (on the right) of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals, $n=6$). The ordinate indicates the percentage change produced by drug administration. Vertical bars show 95% confidence intervals, calculated at each dose.

describe how the energy repartition according to the frequency was changed by the administration of a drug.

The present methodology subtracts the effect of vehicle from the effects of drug (Sebban *et al*., 1999a, b) in order to reduce day-to-day variation. Nevertheless, the EEG changes are complex and it is possible that some subtle vehicle-drug interactions may remain. The methodology has shown utility in predicting effects in man, because S 16924, a clozapine-like agent, increased EEG power in the prefrontal cortex with a peak at 8 Hz in rats (Millan *et al*., 1998): the drug also increased EEG power at 8 Hz in the prefrontal cortex in man in a dose-dependent manner (Macher *et al*., 2000). Furthermore the EEG changes in the rat of clozapine and S 16924 are tightly linked to their plasma levels (Parker *et al*., 2001). The increase in prefrontal cortex theta rhythm (8 Hz) which was seen with S 16924, and to a certain extent with all antipsychotics tested, other than M 100907 (Sebban *et al*., 1999a, b), is of interest because theta rhythm may be linked to cognitive processes (Siapas *et al*., 2000).

The dose-dependent effects of PCP on the EEG, extend the findings of Mattia & Moreton (1986). The synchronization at low frequencies and desynchronization at higher frequencies is unique in our exploitation of this model, where more than 50 drugs have been studied. Furthermore the effects of PCP were obtained with very low doses. What could cause such marked effects on the EEG?

PCP is a NMDA antagonist which causes some increase in dopamine in the prefrontal cortex as evidenced in many models (Freedman & Bunney, 1984; Hondo *et al*., 1994; Jentsch *et al*., 1997a, b; 1998a, b; Verma & Moghaddam, 1996), but this may result from a balance of locally increased release, with reduced activity in the ventral tegmental projections (Takahata & Moghaddam, 1998). As D_2 antagonists are poor antagonists of ketamine in man, other transmitters may be important.

PCP liberates 5-HT (Maurel-Remy *et al*., 1995; Gorelick & Balster, 1994). Cortical 5-HT release in turn liberates glutamate, activating NMDA and AMPA receptors (Aghajanian & Marek, 1997; 1999; 2000). Long-term changes in NMDA and kainate receptor binding follow administration of PCP (Tomita *et al*., 1995; Gao & Tamminga, 1996). The activation of the EEG is intense (>5 fold), despite the low doses of PCP and MK 801 used in this report. Neuronal activation from chronic treatment with PCP, ketamine and MK 801 may be so intense that the compounds cause neurodegeneration in specific limbic tracts (Ellison & Switzer, 1993; Ellison, 1994; 1995; Wozniak *et al*., 1996). Thus the effects of PCP are secondary to changes in glutamate, dopamine and 5-HT.

The increase in EEG power at low frequency is associated with increases in synchronization, and these effects are resistant to all the drugs used in the present study, so the mechanism of action cannot be defined. Nevertheless, this effect is the inverse of the AMPA antagonist, GYKI 52466, which reduced sychronization at very low frequencies. In contrast, EEG power is reduced by PCP at higher frequencies, and over the frequency range 5–20 Hz, PCP, at 1*versus*, resembles modafinil (Sebban *et al*., 1999a, b), a drug marketed for the treatment of narcolepsy, and which increases vigilance and prevents sleep. This second effect of PCP may therefore be associated with hypervigilance, which has been claimed to be a part of schizophrenia: it is this effect

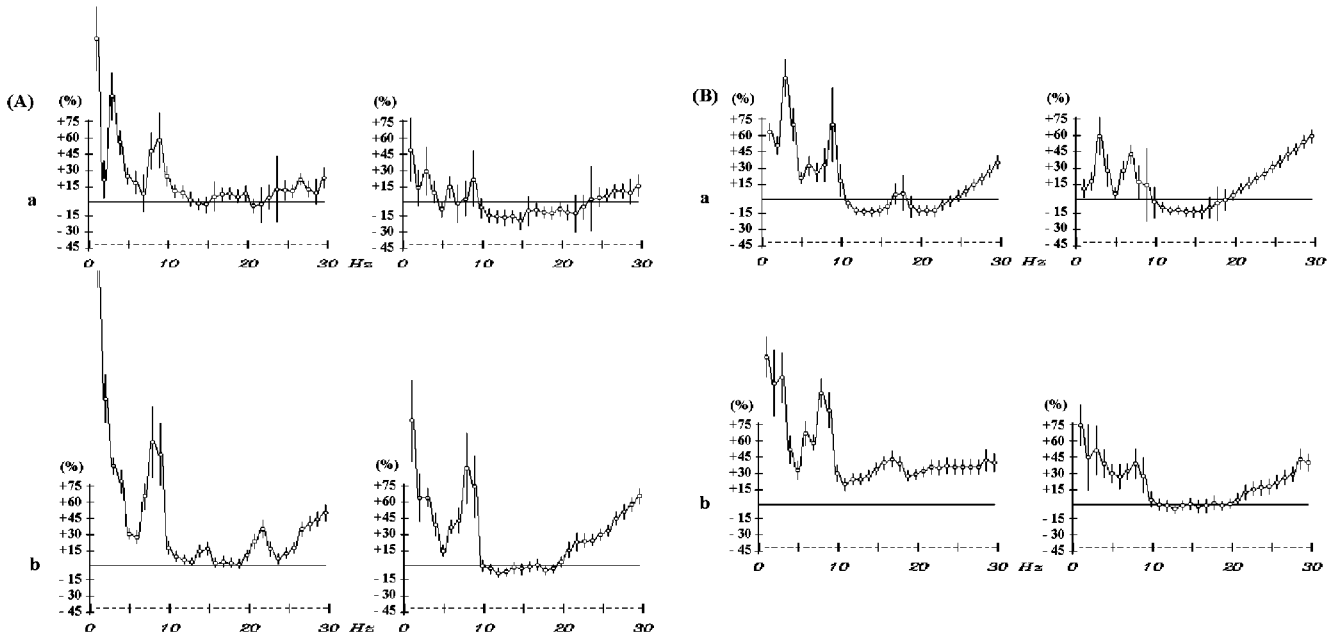

Figure 9 Co-administration of PCP (1 mg kg^{-1} s.c.) and M100907 (A) (0.01 (a), and 0.05 (b) mg kg^{-1} s.c.), PCP (1 mg kg^{-1} s.c.) and prazosin (B) (0.05 (a) and 0.1 (b) mg kg^{-1} i.p.) expressed as per cent change of EEG spectral power in the prefrontal cortex (on the left) and sensorimotor cortex (on the right) of conscious rats (ordinate) at each frequency between 1 and 30 Hz (abscissa). Vertical bars represent 95% confidence intervals, $n=6$). The ordinate indicates the percentage change produced by drug administration.

which is antagonized by the antipsychotic agents. The effects of modafinil were also selectively antagonized by prazosin and clozapine (Sebban *et al*., 1999b). Synchronization between prefrontal and posterior association cortex during working memory tasks in humans enhances coherence over 4–7 Hz (Sarnthein *et al*., 1998): these frequencies are disrupted by PCP. MK-801 was less effective in this regard.

M100907, at doses which would be highly selective for 5-HT_{2A} receptors, caused a pronounced and very specific increase in EEG power, but only at 2 Hz; high doses, which would not be expected to be selective, resulted in a power spectrum similar to that of clozapine. Thalamic and cortical neuronal activities are under the control of cholinergic, serotoninergic, histaminergic, GABAergic and noradrenergic modulatory systems (Steriade *et al*., 1993a, b). Thalamic relay neurons display rhythmic bursts consisting of oscillation in the frequency range of 0.5–4 Hz and spindle oscillations in the frequency range 7–14 Hz (Steriade *et al*., 1993c) during slow-wave sleep. The specific effects of M100907 at 2 Hz may therefore be due either to effects on thalamocortical coupling (Brandenberger *et al*., 1996) or to a local effect on the frontal pyramidal cells, as has been shown *in vitro* by Marek & Aghajanian (1994; 1996; 1998, 1999; Aghajanian & Marek, 2000). The 'clozapine-like' profile of M100907 at the highest dose tested is presumably due to the dose being sufficiently high for the selectivity at 5-HT_{2A} receptors to be lost. If the effect at 2 Hz is local and due to antagonism of locally released 5-HT, or even of dopamine (Schmidt & Fadayel, 1995), then the effects of 5-HT at 5-HT_{2A} receptors have remarkable specificity for the 2 Hz frequency, which may be a useful index of specific events in the cortex mediated by 5-HT.

M100907, at low doses, abolished the desynchronization, over 8–30 Hz, which was induced by PCP, providing further evidence that the effects of PCP are at least partially dependent on 5-HT release. M100907 is a highly potent antagonist of PCP-induced locomotion (Maurel-Remy *et al*., 1995). M100907 has also been reported to antagonize the MK801-induced changes in prepulse inhibition (Varty *et al*., 1999). M100907 has not been found to be active during clinical trails in schizophrenia, although beneficial effects in small patient populations may occur. Previous EEG studies have claimed that serotinergic blockade alone may not yield large effects, but considerable effects may occur in the presence of changes in other transmitter systems, such as in association with cholinergic blockade (Dringenberg & Zalan, 1999). Our findings of small, but highly specific, EEG changes following selective 5-HT_{2A} antagonism, associated with a capacity to antagonize some of the effects of PCP is therefore in line with previous findings and with the limited antipsychotic efficacy of M100907.

Some hallucinogens have affinity for 5-HT2 receptors and have direct effects on cortical pyramidal neurones and associated interneurones (reviewed by Aghajanian & Marek, 2000). These studies may form a bridge between *in vitro* electrophysiology and the more complex phenomena involved in EEG recording. In *in vitro* studies, 5-HT induces excitatory postsynaptic potentials in layer V cortical pyramidal cells (Aghajanian & Marek, 1997; 2000), inducing asynchronous excitatory transmission by 5-HT_{2A} receptors (Aghajanian & Marek, 1998; Marek & Aghajanian, 1998), located on GABAergic interneurones (Gellman & Aghajanian, 1994). Hallucinogens such as lysergic acid, act as partial agonists on 5-HT_{2A}-receptors, and cause a local release of glutamate in the prefontal cortex (reviewed in Aghajanian & Marek, 2000). PCP and DOI can also induce 5-HT release as well as blocking NMDA receptors, by a different mechanism, probably involving glutamatergic thalamic inflow (Aghajanian & Marek, 2000).

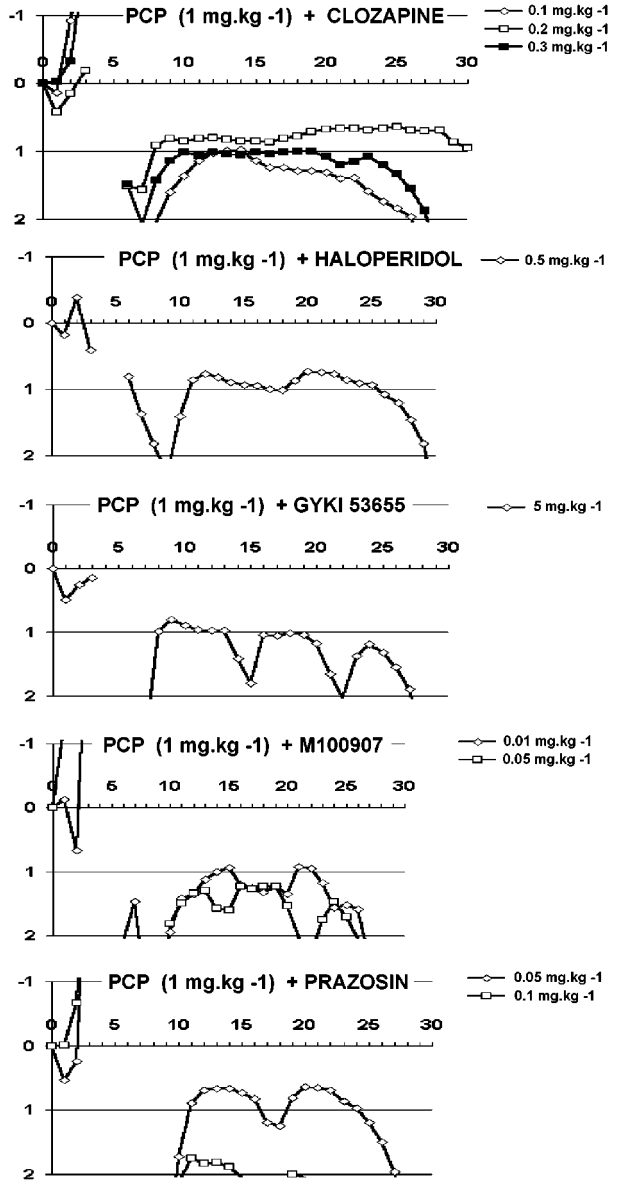

Figure 10 Graphical representation of the attenuation of PCP (1 mg kg^{-1} s.c.) effects in prefrontal cortex when, from top to bottom, clozapine (0.1, 0.2 and 0.3 mg kg^{-1} s.c.), haloperidol (0.5 mg kg^{-1} i.p.), GYKI 53655 (5 mg kg^{-1} i.p.), M100907 (0.01 and 0.05 mg kg^{-1} s.c.) and prazosin (0.05 and 0.1 mg kg^{-1} i.p.) were co-administered. Attenuation (in ordinate) was estimated as described in methods at each frequency between 1 and 30 Hz (abscissa). Zero value corresponds to no change; values less than one to an amplification of PCP effects, Value equal to unity correspond to a full antagonism of the effects of PCP; values >1 to an inversion of PCP effects. Values are not shown where there was no significant modification of the effects of PCP.

The 5-HT release causes further glutamate release (acting on AMPA receptors, Svensson, 2000), which can also be modified by α_1-adrenoceptors (Aghajanian & Marek, 2000).

Hallucinogens generalize to PCP cues in drug discrimination paradigms (West *et al*., 2000). Methylated 5-HT metabolites, such as dimethyltryptamine (DMT) which are hallucinogenic and propsychotic (Pomilio *et al*., 1999), have been detected endogenously in early stage schizophrenic patients and have been claimed to play a role in the symptoms and delusions in the early stages of schizophrenia, in a manner similar to exogenous PCP (Ciprian-Olliver, 1991; Ciprian-Ollivier & Cetkovich-Bakmas, 1997; Pomilio *et al*., 1999).

The AMPA antagonists GYKI 52466 and 53655 showed clear dose-dependent increases in EEG power; GYKI 52466, which is a less specific AMPA antagonist than GYKI 53655 (Maj *et al*., 1995; Vizi *et al*., 1996), showed effects over a wider range of frequencies. The doses which modified EEG in the prefrontal cortex are identical to the doses active in antagonising AMPA receptors and in inducing anti-epileptic effects (reviewed in Vizi *et al*., 1996). The higher doses required to change power spectra in the sensorimotor cortex are similar to the doses required to induce ataxia and muscle relaxant effects. Differential effects on EEG in prefrontal and sensorimotor cortex may be a useful means of screening AMPA antagonists with reduced ataxic effects. GYKI 53655 is more selective for AMPA receptors than GYKI 52466. We are currently investigating whether the difference between the EEG effects of GYKI 52466 and those of GYKI 53655 represents a component of antagonism of kainate receptors.

The AMPA antagonists inhibited the reduction in EEG power caused by PCP in the prefrontal cortex, which may be due to inhibiting aspects of the hyperglutamatergic drive, compatible with the *in vitro* data of Aghajanian & Marek (2000). Takahata & Moghaddam (1998) showed that AMPA antagonists blocked stress- and PCP-induced dopamine release in the prefrontal cortex. Svensson (2000) has proposed that AMPA antagonists may be clinically useful as atypical antipsychotic agents. The present study shows that the effects of PCP in the prefrontal cortex may be inhibited by AMPA antagonists at doses where the drugs alone exert relatively little effect, implying that there is some measure of a selectivity window for antipsychotic effects over the well defined ataxic effects. Neverthess, the inhibition of PCP-induced changes in EEG power may be highly indirect, and not necessarily *via* local changes in the prefrontal cortex.

Global EEG activity reflects a variety of oscillations generated in the thalamus and cerebral cortex (Bradshaw *et al*., 1983; Steriade *et al*., 1990a, b; 1991; 1993a, b, c). Consequently, the precise changes in EEG following the administration of dopaminergic, serotinergic, and glutamatergic agonists and antagonists are complex to interpret. Furthermore, there are very complex interactions between 5-HT, dopamine and noradrenaline release in the frontal cortex of conscious rats (Tassin *et al*., 1992; Gobert *et al*., 1998) as well as in anaesthetized rats (Berridge & Morris, 2000) which will be exacerbated by the administration of such a powerful stimulant as PCP. Nevertheless, when agonists and antagonists of the same receptor type were co-administered, a dose-dependent interaction can be shown on EEG (Sebban *et al*., 1999a, b; 2000). Pharmacological interventions causing a decrease of dopaminergic or noradrenergic transmission induce an increase of EEG spectral power, whereas an increase in dopaminergic or noradrenergic transmission induces a decrease of EEG spectral power (Sebban *et al*., 1999a, b).

The effects of PCP were most effectively antagonized by clozapine, a drug which modulates noradrenergic, dopaminergic and serotoninergic transmission. However, the increase in low frequency power was resistant to clozapine. Nevertheless, the potent effects of M100907 reinforce the importance of 5-HT_{2A} receptors in the prefrontal cortex.

The effects of the antagonists were much more difficult to quantify in the sensorimotor cortex, presumably because of multiple motor interactions. Prazosin blocked some of the effects of PCP, consistent with the finding that many antipsychotic agents have α_1-adrenoceptor blocking effects, and consistent with the antagonism of a 'hyper-attentional state' proposed by Sebban *et al*. (1999b).

Even though, when administered alone, clozapine, the AMPA antagonists GYKI 52466 and 53455, prazosin and M100907 had highly distinctive EEG 'fingerprints', all the drugs caused similar antagonism of the effects of PCP, showing that antipsychotic mechanisms converge at the thalamocortical level, supporting the propositions of Aghajanian & Marek (2000). The present model would seem to be useful for the profiling of antipsychotic drugs and has been partially validated in man.

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