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Effects of Highly Selective κ-Opioid Agonists on EEG Power Spectra and Behavioural Correlates in Conscious Rats

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COLTRO CAMPI, C. AND G. D. CLARKE. *Effects of highly selective κ-opioid agonists on EEG power spectra and behavioural correlates in conscious rats.* PHARMACOL BIOCHEM BEHAV 51(4) 611–616, 1995.—The present study compares the electroencephalographic (EEG) and behavioural effects of highly selective κ-opioid agonists, spiradoline (U62066), enadoline (CI-977), BRL 52656, and BRL 53001, after SC administration to conscious rats. All compounds caused a distinctive dose- and time-related EEG effect and behavioural profile. The EEG power spectra (PS) of treated animals were characterised by power reduction indicative of CNS activation and an unusual spectral peak at 4–7 Hz, compared to controls. Behaviourally, however, the animals appeared to be sedated, with a reduction of locomotor activity, loss of postural tone, ataxia, and unusual hyperreactivity. The compounds differed in their liability to produce these CNS effects, with κ-opioid analgesics such as enadoline and BRL 53001 showing a reduced propensity at equivalent antinociceptive doses. Where tested, these effects were inhibited by the nonselective opioid antagonist naloxone. The non-brain penetrating κ-opioid agonist, BRL 52974, failed to produce alterations in EEG PS or behaviour, up to a dose of 10 mg/kg, indicating that the effects depend on activation of centrally located κ-receptors.

κ-Opioid agonists EEG power spectra Behaviour Rats

IN RECENT years, the search for a novel, strong analgesic lacking the side-effects of existing μ-opioid therapies has concentrated on the evaluation of κ-opioid analgesics [for a review see (21,27)]. Highly selective, brain-penetrating κ-opioid agonists produce antinociception in a range of animal models (11,13,32,33,39). Administration of κ-agonists, however, is also associated with a number of other effects including diuresis, locomotor impairment, sedation, and aversion (1,3,11,13, 15,21,39); these effects depend on the compound being able to penetrate the blood–brain barrier (BBB) (3).

Clinical data with the selective κ-agonist spiradoline (U62066) indicate that it produces analgesia following dental surgery, but also produces altered perception, diuresis, sedation, and psychotomimetic effects at similar doses (9,23,24). Similar behavioural effects had been previously reported with the nonselective κ-agonists ketocyclazocine (14) and the benzomorphan MR2033 (25). More recently, the very highly selective κ-agonist enadoline (CI-977), which is reported to be under development as an analgesic, has also been shown to produce various CNS effects (7,27). Electroencephalography has been used extensively to assess the effects of CNS-active compounds on the electrical activity of the brain (8,12,35). The recent application of power spectral (PS) analysis of analogue electroencephalographic (EEG) data has allowed some degree of quantification of these CNS effects, and distinct patterns of activity have been seen for agonists acting—for example, at opioid and σ-receptors (2,17–19,22,28–31,34–37).

Studies with early κ-agonists, including ethylketocyclazocine, ketocyclazocine, and U-50,488H revealed EEG PS that were characterised by high-voltage (HV) EEG bursts and a predominant spectral peak in the 4–6-Hz band (22,30,35,36) associated with behaviourally stuporous animals.

Psychotomimetic-like behavioural effects (sniffing, backward movements, extensive periods of stillness) and EEG effects (EEG desynchrony with increase of the spectral power over the 0–10 Hz range, including a relatively small peak at 4–6 Hz) were reported in some studies, but were probably due to a σ-component in the κ-agonists studied (U-50,488H) (34,

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36,37). Studies with the more selective κ-opioid agonist PD117302 revealed a distinct EEG "fingerprint" that featured a single spectral peak centered around 4–5 Hz, associated with an immediate flaccid immobility-cataleptic state, which failed to produce a psychotomimetic profile (31).

The present study was performed to examine the EEG PS and behavioural profiles of more recently discovered, selective κ-agonists and to establish their liability to produce these effects at equivalent antinociceptive doses. Specifically, the κ-agonists considered in this study were spiradoline (33), enadoline (13), BRL 52656 (5,6), BRL 53001 (10,39), and BRL 52974 (3).

METHOD

Animals

Experiments were performed using male Sprague-Dawley rats (Charles River, Calco, Italy) weighing between 300 and 320 g on the day of electrode implantation. Prior to surgery, the rats were housed in groups of five animals per cage at 22 ± 1°C and were maintained under a 12 L : 12 D cycle; they received food and water ad lib. Following implantation of the electrodes, the animals were maintained in individual cages that served as their home cage throughout the experimental period; otherwise, animal housing conditions were the same as described earlier. Experiments were performed during the light phase (0900–1700 h) and different groups of animals (n = 4–6) were used for each compound tested. Unless indicated otherwise, separate animals were used for each dose tested; each rat was used only once.

Surgical Procedures

Following general anaesthesia with sodium pentobarbital (40 mg/kg IP), the heads of the animals were fixed using a stereotaxic frame and two epidural stainless-steel screw electrodes were chronically implanted in the skull above the ipsilateral frontal (2 mm anterior to the bregma and 2 mm lateral to the midline) and parietal (4 mm posterior to the bregma and 2 mm lateral) cortex (30). The electrodes were fixed in place using acrylic dental cement, and the animals were allowed to recover for at least 1 week. Antibiotic (Velamox SB Farmaceutici, Milan, Italy) was administered after surgery to prevent infections.

EEG Recording and Power Spectral Analyses

On the day of the study, animals were connected by two flexible cables to a Neuroscript EE112 polygraph (PPG Hellige, Milan, Italy) for continuous collection of analogue data. Animals were allowed to acclimatise in an isolated procedure room for about 3–4 h before experimentation.

The cortical EEG was filtered at the polygraph at 30 Hz with a time constant of 0.1 s. On-line fast Fourier transformation (FFT) for 10-s epochs of the analogue EEG data was performed using a CED 1401 (Cambridge Electronic Design Limited, Cambridge, UK) Laboratory Interface, connected to an IBM PC XT 286 (each epoch comprised 1024 points). For each animal, off-line analysis was performed using custom software (CEDAR) (20) by averaging 18 sequential, artefact-free, 10-s epochs.

Prior to drug administration, control power spectra were obtained for a) quiet-awake, b) continuous-sleep, and c) REM-sleep periods. To standardise the PS of individual animals before experimentation, the absolute power values during the predrug quiet-awake state were adjusted for each rat, to give 1000 μV^2 total power.

Following drug administration, periods of 3–4 min recording were taken at 15- or 30-min intervals (t_{15}, t_{30}, t_{60}, t_{90}). Drug-induced changes in the EEG PS (1–30 Hz) were calculated as percentage (relative PS) using the quiet-awake predrug PS for each rat as the control baseline (0% level). All absolute and relative EEG PS are expressed as mean (± SEM).

Behavioural Rating

Behavioural observations were made concurrently with the EEG recordings using a Philips (Italy) videocamera and a remote monitor. A behavioural rating scale (Table 1) was specifically developed to quantify the three main behavioural components (i.e., locomotor activity, ataxia/postural tone, and reactivity) that were characteristically seen following administration of κ-opioid agonists. Rating levels of I and I+ referred to control animals, whereas κ-related behavioural patterns were quantified using levels II, III, and IV.

Drug Administration

The test drugs were administered SC into the midclavicular region to hand-restrained animals, and all compounds were administered between noon and 1300 h. The following drugs were given, all dissolved in saline and administered at room temperature in a final volume of 1 ml/kg body wt.: spiradoline (1.5, 6, and 22 mg/kg), enadoline (0.015 and 0.2 mg/kg), BRL 52656 (0.24, 1, and 3.7 mg/kg), BRL 53001 (1.5 and 22 mg/kg), and BRL 52974 (10 mg/kg). All of these compounds were synthesised at SB Farmaceutici (Milan, Italy).

In antagonism studies naloxone (Salars, Italy) was administered at 1 mg/kg SC either together or after the test compound. All doses are expressed as pure free base.

RESULTS

The control EEG recordings made during the predosing, behavioural states of wakefulness, continuous sleep, and

TABLE 1

RATING SCALE FOR THE BEHAVIOURAL SYNDROME INDUCED BY ADMINISTRATION OF HIGHLY SELECTIVE KAPPA OPIOD AGONISTS TO CONSCIOUS RATS

I	Generally stationary, inactive or in-place activity with coordinated movements. Normoreactive to external stimuli. Tendency to sleep.
I+	Predominant sleep with REM-sleep periods.
II	Predominant inactivity. Jerky movements, ataxia. Partial impairment of postural reflexes. Sudden arousal periods with escape attempts.
III	Extensive periods of stillness, with occasional catatonic (same maintained position for >3 min) posture. Increased ataxia. Animals may support weight on haunches and abdomen. Hyperreactivity to mild external stimuli.
IV	Highly catatonic immobility. Almost unable to move. Supporting weight only on haunches and abdomen. Non reactive to external stimuli (stuporous).

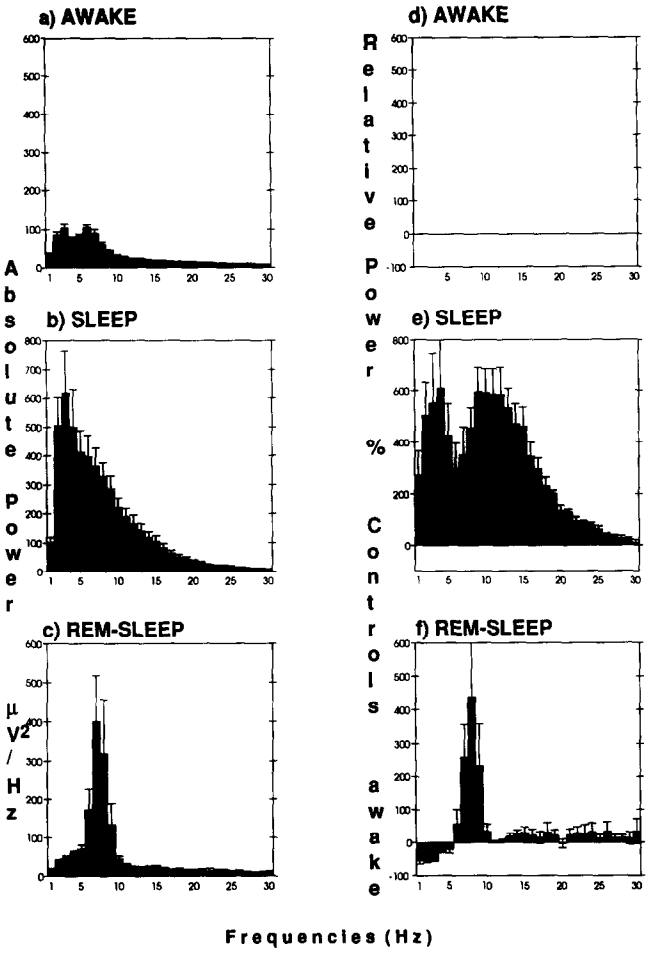

FIG. 1. Mean power spectra (1-30 Hz) derived from cortical EEG during predosing control periods. In (a) and (b) (n = 6) and (c) (n = 3), PS are expressed as standardized, absolute values (power: μV^2/Hz). In (d-f), the same spectra have been transformed in relative values (power: percent predrug controls awake).

REM-sleep produced absolute PS that were similar to those previously described by other workers (30,38) (Fig. 1a-c).

The quiet-awake related spectrum was characterised by low power values, compared with either sleep or REM-sleep, and the power was almost equally distributed over the 1-10 Hz range. Continuous sleep was associated with a large increase in spectral power that was higher at the lower frequencies and then decreased linearly as frequency increased above 3-4 Hz. REM-sleep was characterised by a predominant peak of spectral power in the 7-9 Hz range. The relative PS—obtained by expressing the sleep and REM-sleep absolute values as a percentage of the awake PS—are shown in Fig. 1d-f. In addition to demonstrating the marked power increase, the relative PS associated with continuous sleep had a different power distribution characterised by a twin peak around 3-4 and 10-14 Hz with a gradual power diminution at higher frequencies. The profile of the relative PS associated with REM-sleep, besides a power reduction in the δ-frequency band (1-4 Hz), was very similar to the absolute PS.

At equianalgesic doses, equivalent to approximately six times the antinociceptive ED_{50} in the rat abdominal constriction (RAC) test (39), clear differences were seen in the EEG PS and behavioural profiles of the κ-agonists studied (Fig. 2). Spiradoline (1.5 mg/kg) and BRL 52656 (0.24 mg/kg) produced similar effects, characterised by an EEG PS of similar overall power values to those seen in the control awake state, with the exception of the appearance of a spectral peak frequency at 5 Hz. This PS profile was derived from a low-voltage (LV) analogue trace, which showed an unusually high incidence of sinusoidal (θ) activity at 5 Hz. Compared to time-matched saline-treated animals, both spiradoline and BRL 52656 reduced EEG power with an associated reduction in the sleep periods and appearance of behavioural symptoms (rating II). These symptoms included prevalent periods of immobility (with partial loss of postural tone and slightly catatonic postures) that were suddenly interrupted by occasional, ataxic attempts to escape from the cage in the absence of external stimuli. At equivalent antinociceptive doses, BRL 53001 (1.5 mg/kg) and enadoline (0.015 mg/kg) failed to produce appreciable behavioural effects (rating index I) apart from a reduced tendency to sleep, compared to saline-treated rats. Their EEG spectral profile was close to the baseline, with

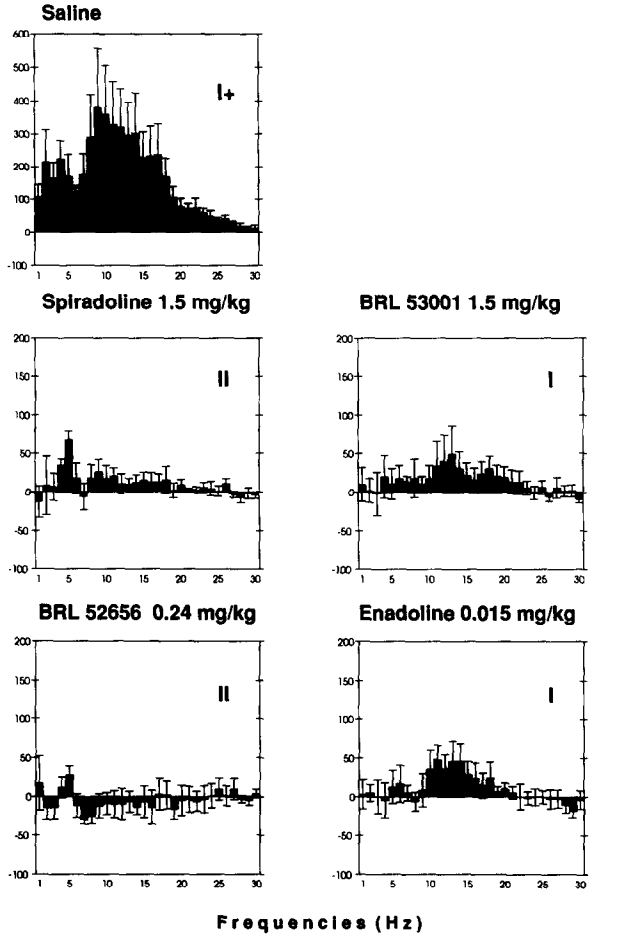

FIG. 2. Mean relative PS (power: percent predrug controls awake) and behavioural indices (see Table 1) obtained 30 min after SC administration of saline (n = 6) and four highly selective κ-agonists (n = 4) at doses equivalent to six times the RAC ED_{50}.

only a low-power increase around the middle region of the spectrum (10–20 Hz), similar to that seen in saline-treated animals.

Administration of higher doses of the κ-opioid agonists (equivalent to 25–30 times the RAC ED_{50} for BRL 52656 and spiradoline and 90 times for BRL 53001 and enadoline) produced EEG PS profiles that were qualitatively similar, even if quantitative differences were still apparent among the compounds (Fig. 3). Overall, the power values were low, often below the baseline obtained during the predrug awake state. All of the compounds caused a clear peak frequency around 5 Hz. The behavioural rating indices (III) were similar for all compounds and reflected the magnitude of the effects of the compounds on the EEG PS. These behavioural effects were characterised by marked ataxia and loss of postural tone, with the animals lying for long periods maintaining the same catatonic posture. The animals were, however, hyperreactive to mild external mechanical or auditory stimuli, exhibiting biting, crying, or jumping behaviour.

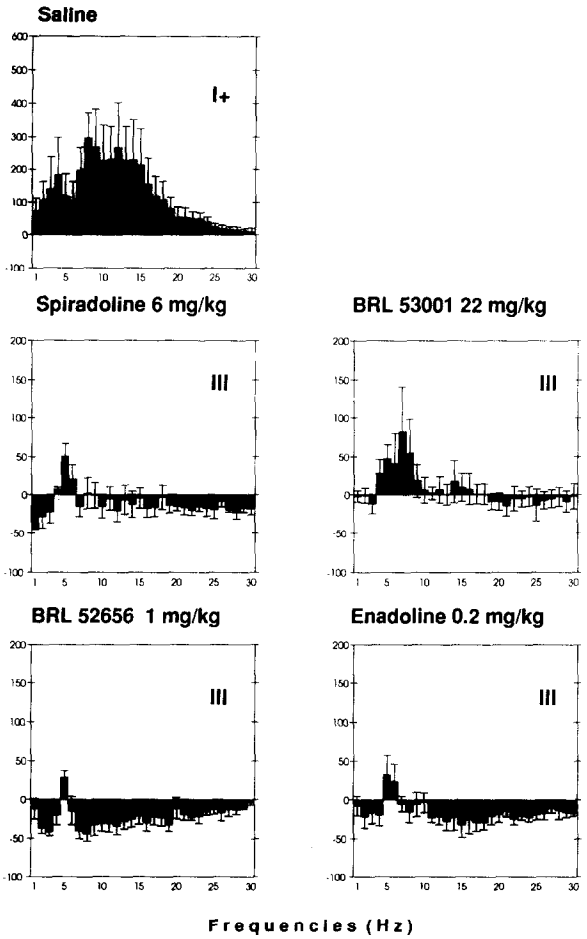

FIG. 3. Mean relative PS (power: percent predrug controls awake) and behavioural indices (see Table 1) obtained 30 min after SC administration of saline (n = 6) and four highly selective κ-agonists (n = 4) at doses equivalent to 90 times the RAC ED_{50} (BRL 53001 and enadoline) and 25–30 times the RAC ED_{50} (BRL 52656 and spiradoline): BRL 52656 and spiradoline were administered to animals that had received a lower dose (six times the RAC ED_{50}) of compound 90 min previously.

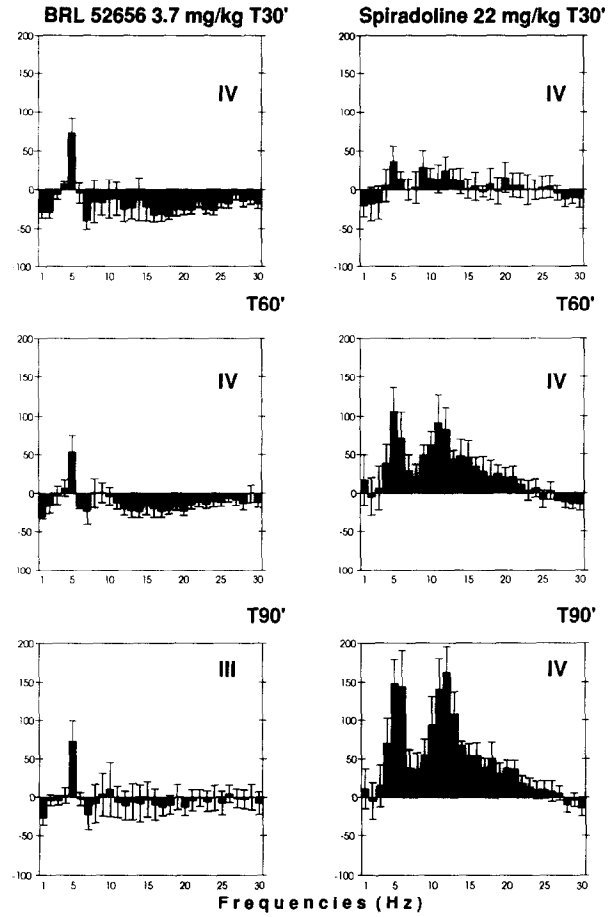

FIG. 4. Mean relative PS (power: percent predrug controls awake) and behavioural indices (see Table 1) after SC administration of approximately 100 times the RAC ED_{50} dose of BRL 52656 and spiradoline (n = 4).

Figure 4 shows the time-related PS obtained after administration of BRL 52656 (3.7 mg/kg) and spiradoline (22 mg/kg) to naive rats at doses equivalent to approximately 100 times the RAC ED_{50}. BRL 52656 caused a marked spectral peak at 5 Hz with overall low-power values. These effects could be seen about 5 min after drug administration and were maintained (with a time-dependent decrease) up to 90 min. Spiradoline, however, at this high dose produced a delayed increase of power characterised by a double peak at 4–6 and 10–13 Hz. This PS was derived from the appearance of regular, sinusoidal-like, high-voltage (HV) spike-wave bursts, superimposed on a background LV trace, which maintained a 5-Hz rhythm. Behaviourally, both compounds induced the highest rating level (IV) of ataxia, loss of postural tone, catatonia, and stupor. At similar equivalent antinociceptive doses (Fig. 3), enadoline (0.2 mg/kg) and BRL 53001 (22 mg/kg) caused an EEG fingerprint that closely resembled that of BRL 52656.

At a dose of 1 mg/kg SC, the nonselective opioid antagonist naloxone antagonised the effects of 1 mg/kg BRL 52656 when given concurrently (Fig. 5a and b), and reversed the effects of BRL 52656 given 30 min previously (Fig. 5d and e). At this dose, naloxone alone (Fig. 5c) produced no obvious

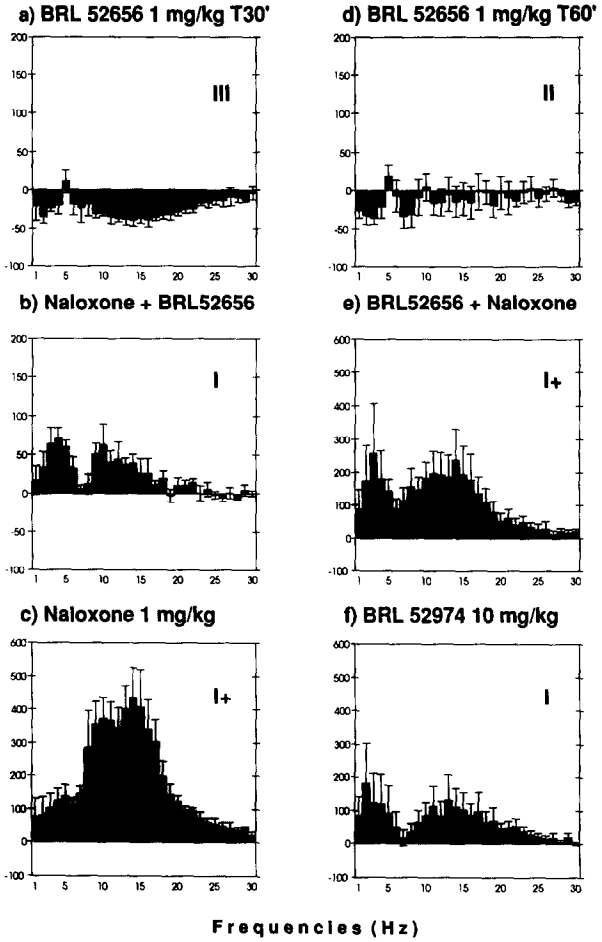

FIG. 5. Relative PS (power: percent predrug controls awake) and behavioural correlates (see Table 1) obtained: (a) 30 min and (d) 60 min after administration of BRL 52656 (1 mg/kg); (b) 30 min after coadministration of naloxone (1 mg/kg) and BRL 52656 (1 mg/kg); (e) 30 min after administration of naloxone (1 mg/kg) given 30 min after BRL 52656 (1 mg/kg); (c) 30 min after naloxone (1 mg/kg); and (f) 30 min after administration of BRL52794 (10 mg/kg). Means ± SEM of four rats per group.

EEG or behavioural effects compared to saline-treated control animals (Figs. 2 and 3). Naloxone also antagonised the effects of BRL 53001 (22 mg/kg; data not shown).

Finally, in a separate series of experiments to determine the locus of action of the κ-effects seen earlier, a study was carried out using BRL 52974. This highly potent, highly selective κ-agonist has limited ability to cross the BBB (3). At 10 mg/kg SC, BRL 52974 was without significant EEG or behavioural effects, as can be seen in Fig. 5f.

DISCUSSION

Our study shows that administration of highly selective κ-opioid agonists to chronically implanted, conscious rats causes characteristic dose- and time-related profiles in terms of EEG and behavioural effects.

The κ-induced EEG profile was characterised by an LV trace, showing an unusually high incidence of θ-rhythm at 5 Hz. The power spectra obtained by fast Fourier transformation of the analogue EEG trace showed power values at or below those obtained from quiet-awake animals, indicating CNS activation. In addition, there was the emergence of a spectral peak at 4–7 Hz, as noted by other workers with this class of compounds (31).

Very high doses of spiradoline (22 mg/kg) evoked delayed, regular, sinusoidal-like HV bursts, as noted by other workers with ketocyclazocine, U-50,488H, and spiradoline (34–37). However, in the present study, equivalent antinociceptive doses of BRL 52656 failed to produce these HV effects. We are thus unable to confirm that the HV effect is part of a more generalised κ-induced EEG profile. The κ-induced behavioural correlates were in good agreement with data from the literature (1,31,36), and dose-related increases in three main behavioural patterns (reduction of locomotor activity, increasing ataxia with loss of postural tone, and altered reactivity to external stimuli) were noted. To quantify these three behaviours, we created a specific rating scale that may prove useful in future behavioural studies with this class of compound.

In both animals and humans, κ-agonists have been reported to produce sedation (11,13,16,21,23,39). Indeed, a superficial behavioural examination of the rats in the present study would seem to confirm this idea. However, the lack of movement of the rats in this and other studies is more likely to be due to an ataxic, rather than sedative action of the κ-compounds. Indeed, the EEG profile—i.e., an LV EEG—is indicative of central activation rather than depression (8). In addition, the animals were behaviourally hyperreactive to external stimuli and, following low doses of κ-agonists (which did not compromise locomotion), showed very unusual escape attempts from the home cage, as also reported by other authors (1). This syndrome of ataxia and CNS activation has indeed been seen in clinical studies with BRL 52656, in which a reduction of finger-tapping frequency but an increase in flicker-fusion frequency was noted (K. Eckel, personal communication).

In summary, with the exception of BRL 52974, a κ-agonist with limited ability to cross the BBB (3), all of the highly selective κ-opioid agonists tested caused similar, characteristic, dose-related effects on EEG and behaviour. However, quantitative differences were observed among the compounds in terms of their propensity to produce EEG and behavioural effects at equivalent antinociceptive doses. Compounds such as enadoline and BRL 53001 seem to have reduced potential to produce adverse CNS effects at analgesic doses compared to BRL 52656A and spiradoline. The reason for the differential activation of effects is unclear, but it may be related to stimulation of different receptor subtypes (4). It remains to be seen whether these preclinical findings can be confirmed in therapeutic trials to identify a safe κ-analgesic.

Naloxone antagonised the EEG and behavioural effects of BRL 52656 and BRL 53001. Because binding data (10,32) indicate that these compounds are selective for the κ-subtype of opioid receptor, it can be assumed that κ-opioid receptors are involved in these effects. Furthermore, because the non-brain penetrating agonist BRL 52974 was without EEG and behavioural effects, a central locus of action is implicated.

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