Response-Rate Suppression in Operant Paradigm as Predictor of Soporific Potency in Rats and Identification of Three Novel Sedative-Hypnotic Neuroactive Steroids

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Accepted for publication August 31, 1999 This paper is available online at http://www.jpet.org

ABSTRACT

Novel neuroactive steroids were evaluated for their effects on operant responding, rotorod motor performance, and electroencephalogram recording in rats. Co 134444, Co 177843, and Co 127501 were compared with the prototypical γ-aminobutyric acid A-positive allosteric modulators triazolam, zolpidem, pentobarbital, pregnanolone, and CCD 3693. Each of the compounds produced a dose-related decrease in response rates under a variable-interval 2-min schedule of positive reinforcement in an operant paradigm. In addition, all compounds produced a dose-related increase in ataxia and significant increases in nonrapid eye movement sleep in this experiment or have been previously reported to do so. Co 134444, Co 177843, and Co 127501 increased nonrapid eye movement sleep at doses that had no effect on rapid eye movement sleep. All of the compounds were more potent at decreasing operant responding than they were at increasing ataxia. Furthermore, the potency of compounds to produce response-rate suppression in an operant paradigm appeared to be a better predictor of soporific potency than did potency in the rotorod assay. The screening for sedative-hypnotic activity resulted in the identification of the novel orally active neuroactive steroids Co 134444, Co 177843, and Co 127501.

Insomnia is often inadequately treated even though it affects approximately 36% of the population (Mendelson and Jain, 1995). The indirect cost of insomnia to society is great, with effects such as reduced workplace productivity, increased industrial accidents and increased motor vehicle accidents (Walsh and Engelhardt, 1994). Thus, the effort to discover novel and effective treatments for sleeping disorders continues. The desired profile of novel sedative-hypnotic therapeutics includes an increase in nonrapid eye movement (NREM) sleep without a decrease in rapid eye movement (REM) sleep and without rebound insomnia (Mendelson and Jain, 1995; Parrino and Terzano, 1996). Electroencephalogram (EEG) recording of increased NREM sleep in animals remains the most meaningful preclinical predictor of a compound's soporific efficacy in humans. Studies involving EEG recording, however, are costly and time consuming. It is common practice, therefore, to use a preliminary screen to narrow the number of compounds for further evaluation on EEG parameters. The rotorod procedure is one such screen and has the advantage of being a relatively rapid evaluation of ataxia, a behavioral effect caused by sedative-hypnotic drugs. Motor incoordination is not a therapeutic target, however, but rather an adverse side effect (Mendelson and Jain, 1995). In fact, the clinically active sedative-hypnotics triazolam and zolpidem, as well as the novel sedative-hypnotic neuroactive steroid CCD 3693, more potently increase NREM sleep than they cause motor impairment in a rotorod procedure in rats (Edgar et al., 1997). This potency discrepancy may interfere with the discovery of a compound that has a desirable wide separation between soporific activity and ataxia, in that a compound that is not potent in the rotorod screen may never be tested further for effects on EEG. Thus, a preliminary screen that could predict not only efficacy but also potency would be useful in the discovery process of novel sedative-hypnotics.

It has been reported previously that benzodiazepine receptor agonists more potently suppressed response rates in an operant task in rats than caused ataxia in a rotorod task in mice (Bayley et al., 1996). Although direct dose comparisons are difficult across species, the study by Bayley and colleagues suggests that sedative-hypnotic compounds may be more potent in an operant task than in a rotorod task, possibly making response-rate suppression in an operant task more predictive of actual soporific potency. Operant para-

ABBREVIATIONS: NREM, nonrapid eye movement; REM, rapid eye movement; CT, circadian time; EEG, electroencephalogram; GABA, γ-aminobutyric acid; MSD, minimum significant dose; SD₅₀, suppressive dose; TD₅₀, toxic dose; VI, variable interval.
digms are extremely sensitive to pharmacologic manipulations and have been used to assess potency relationships of compounds and to differentiate among compounds of similar class (Leander, 1975; Sanger and Benavides, 1993; Burke et al., 1994). In addition, operant paradigms have proved useful in the prediction of clinical efficacy for various psychiatric disorders (Fibiger and Phillips, 1985; Seiden and O'Donnell, 1985; Barrett and Vanover, 1993). Operant behavior requires an initial investment in time to train the animals. However, more frequent testing and the lack of surgery required renders operant behavior more cost and time effective as a screen than relying solely on EEG.

The purpose of our study was first to evaluate the response-rate suppression induced by various sedative-hypnotic agents in a lever-pressing operant task in rats. Second, a comparison of potencies of these compounds across preclinical assays in rats, specifically the operant lever-pressing task, rotorod, and EEG, was conducted. Compounds included a benzodiazepine (triazolam), an imidazopyridine (zolpidem), a barbiturate (pentobarbital), and the neuroactive steroids pregnanolone and CCD 3693 (Fig. 1). In addition, three novel neuroactive steroids, Co 134444, Co 177843, and Co 127501, were identified as potential sedative-hypnotic drugs (Fig. 1).

**Materials and Methods**

All experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals (1996).

**Operant**

**Animals and Apparatus.** Naive male rats (Sprague-Dawley; Harlan Sprague-Dawley, Inc., San Diego, CA) weighing approximately 280 g were housed individually in polycarbonate cages containing sterilized bedding material (Sani-Chips; P.J. Murray, Montville, NJ) in a room maintained at 23.0°C (±2.5°C) and on a 12-h light/dark cycle (lights on 5:30 AM). Food (Harlan Teklad, Madison, WI) was restricted to postsession supplements (approximately 10 g/day) sufficient to maintain stable body weights (±5%) and behavioral performance. Sessions were conducted generally 5 days/week and rats were fed 10 to 15 g food/day on days with no session (i.e., weekends and holidays). Water was freely available in the home cage.

For experimental sessions, rats were placed in sound-attenuating chambers (30 × 24 × 33 cm; Coulbourn Instruments, Lehigh Valley, PA) equipped with two response levers with associated stimulus lights. For this experiment, only the right lever was active. A magazine for the sucrose dipper and its associated light were located between the two levers. Med-Associates (East Fairfield, VT) computer software and interface controlled stimulus events and recorded lever presses.

**Procedure.** Rats (n = 22) were trained to press a lever for a 4-s period of access to a sucrose solution reinforcer (110 g sucrose/l water). This concentration of sucrose has been demonstrated to maintain operant performance (Vanover and Barrett, 1994; Vanover, 1997). Experimental sessions lasted 20 min. Lever pressing was first trained by method of successive approximation. Training then continued under a fixed-ratio 1 schedule of reinforcement in which every lever press was reinforced. When responding was stable, the schedule of reinforcement was changed to a variable-interval (VI) 7-s schedule in which the first lever press after 7 s, on average (range 1–14 s), was reinforced. The interval was increased gradually over sessions with a final VI 2-min schedule of reinforcement in which the first lever press after 2 min, on average (possible intervals of 0, 10, 30, 60, 120, 180, 210, 230, and 240 min), was reinforced. Drugs were tested with a subgroup of 10 to 19 rats.

**Data Analysis.** Response rates (responses per min) were calculated for every session separately for each rat. For test sessions, response rates were calculated as percentage of control, with control defined as the mean of the three previous non-test sessions. Suppression of responding was defined as a decrease to 75% or less of the individual’s control rate of responding. The dose at which the responding of half the rats tested was suppressed was designated as the suppressive dose (SD₅₀). Calculations were based on the method of Litchfield and Wilcoxon with PHARM/PCS version 4.2 software (Springer-Verlag, NY). In addition, the 95% confidence intervals (CIs) were calculated around each SD₅₀.

**Rotorod**

**Animals and Apparatus.** Naive male rats (Sprague-Dawley) weighing 200 to 225 g were housed (two per cage) in polycarbonate cages containing sterilized bedding material (Sani-Chips; P.J. Murray, in a room maintained at 23.0°C (±2.5°C) and on a 12-h light/dark cycle (lights on 5:30 AM). Food and water were freely available in the home cage.

The rotorod test used a custom-built apparatus that consisted of an elevated drum (7.62 cm diameter) of textured surface that rotated at a constant speed (8 rpm). The height of the drum from the floor of the test apparatus was approximately 30 cm.

**Procedure.** Before administration of test substance, rats were trained to walk continuously on the drum for a period of 90 s. During testing, rats were given three opportunities to remain on the apparatus continuously for 1 min. Remaining on the apparatus was scored as a pass. Results were treated quantally.

**Data Analysis.** Each dose-response function (n = 8–26/dose) was based on separate experiments (n = 8–10/dose) conducted on different days and the results summed. A dose that caused behavioral toxicity in half the animals (toxic dose; TD₅₀) was calculated based on each dose-response function by the method of Litchfield and Wilcoxon with PHARM/PCS version 4.2 software (Springer-Verlag). In addition, the 95% CIs were calculated around each TD₅₀.

![Fig. 1. Chemical structures of pregnanolone, CCD 3693, Co 134444, Co 177843, and Co 127501.](image-url)
EEG

Animals and Apparatus. Adult male Wistar rats (Charles River Laboratories, Wilmington, MA) weighing 275 to 350 g at time of surgery were used as subjects. Rats were anesthetized (nembutal, 60 mg/kg) and surgically prepared with a cranial implant that permitted chronic recording of EEG. The cranial implant consisted of stainless steel screws [two frontal (+3.9 anterior/posterior from bregma, ±2.0 medial/lateral) and two occipital (−6.4 anterior/posterior, ±5.5 medial/lateral)]. All leads were soldered to a miniature connector before surgery and chemically sterilized in Glutarex (3M Co., Minneapolis, MN). The implant assembly was affixed to the skull with dental acrylic. A minimum of 3 weeks was allowed for recovery.

Rats were housed individually in specially modified Nalgene microisolator cages equipped with a commutator and filter-top riser. These cages were located within separate, ventilated compartments of a stainless steel cabinet. Food and water were freely available. A 12-h light/dark cycle was maintained throughout the study with 4-W fluorescent bulbs 5 cm from the cage. Animals were undisturbed for 3 days both before and after treatments.

Procedure. Sleep and wakefulness were determined with SCORE, a microcomputer-based sleep-wake and physiological monitoring system. A description and validation for this system for rodents has been previously described (Edgar et al., 1991; Van Gelder et al., 1991). Briefly, the system monitors amplified EEG (band pass 1–30 Hz; digitization rate 100 Hz), among other variables, from 48 rodents simultaneously. Arousal states were classified on-line as NREM sleep, REM sleep, wake, or θ-dominated wake every 10 s with EEG feature extraction and pattern-matching algorithms. Quality of data was ensured by frequent on-line inspection of the signal; also, a graphical and statistical summary of the 3 days before and after each animal’s injection was inspected to determine stability of the scoring. A printout of this 6-day period was inspected for each individual treatment to examine data quality. An integrated relational database was updated with yes/no decisions for data quality of each individual treatment, and this database controlled all subsequent use of these data. Data quality was further ensured by examining the raw EEG file (covering the first 4 h posttreatment) for every individual treatment. All treatments were administered to parallel groups under dim red illumination 6 h after lights-out. This time point is usually designated CT-18 (CT, circadian time; CT-0 = lights on).

Data Analysis. NREM and REM sleep were expressed as percentage of time asleep per hour. The sleep scores were derived from automated scoring, described above. By inspection of the data, if was evident that, for all treatments, primary hypnotic effects (e.g., increased NREM sleep) occurred within the first 4 h. Therefore, for each rat, the average hourly response across the first 4 h posttreatment was subtracted from the corresponding average of the 4-h pretreatment baseline period taken 24 h earlier. This change-from-baseline score was then compared against the appropriate vehicle control with ANOVA. In the presence of a significant main effect, Dunnett’s contrasts were conducted between an active treatment and control with ANOVA. In the presence of a significant main effect, Dunnett’s contrasts were conducted between an active treatment and control with ANOVA. In the presence of a significant main effect, Dunnett’s contrasts were conducted between an active treatment and control with ANOVA. In the presence of a significant main effect, Dunnett’s contrasts were conducted between an active treatment and control with ANOVA.

Drugs

Co 134444 was prepared in two steps from 3α-hydroxy-3β-methoxyethyl-5α-pregnan-20-one (Co 145010; Hogenkamp et al., 1997). Bromination (bromine, catalytic aqueous HBr in MeOH) in 50% overall yield. Co 145010 was dissolved in a solution of 1.45 M HCl. A vehicle of 50:50 (w/v) hydroxypropyl-β-cyclodextrin/0.9% saline (50% HPβCD) was used to dissolve pregnanolone, synthesized by AKZO-Diosynth (Oss, the Netherlands), CCD 3693, Co 177843, and Co 127501, all synthesized by CoCensys, Inc. (Irvine, CA). Co 177843 was prepared from Co 145010 in three steps. Bromination as described for the preparation of Co 134444 gave the 21-bromide, which was treated with 6-hydroxyquinoline and subsequently oxidized to the N-oxide with 3-chloroperbenzoic acid. Co 127501 was prepared in eight steps from 3β-hydroxyprogren-5-en-20-one in overall 24% yield. Pentobarbital sodium, dissolved in 0.9% saline, was obtained from Sigma Chemical Co. (St. Louis, MO). Triazolam, suspended in 0.25% methylcellulose, was obtained from Upjohn (Kalamazoo, MI). Zolpidem, dissolved in 50% HPβCD, was purchased from Research Biochemicals International (Natick, MA). Pregnanolone, triazolam, and pentobarbital were administered i.p. in a volume of 1.0 ml/kg; CCD 3693, Co 134444, Co 177843, and Co 127501 were administered p.o. in a volume of 5.0 ml/kg. Zolpidem was administered both i.p. and p.o. Doses were calculated based on salt forms of the test compounds, where applicable. For operant experiments, triazolam was administered 10 min before the session, whereas pregnanolone, zolpidem (i.p.), and pentobarbital were administered with a pretreatment time of 30 min. Zolpidem (p.o.), CCD 3693, Co 134444, Co 177843, and Co 127501 were administered 15 min before the session. For rotorod experiments, all compounds were administered at time of peak effect: triazolam, 10 min; pentobarbital, 15 min; Co 127501, 60 min; Co 134444, 30 min; Co 177843, 60 min; and zolpidem, 30 min. For EEG experiments, all compounds were administered at CT-18.

Results

Operant. Under a VI 2-min schedule of reinforcement, baseline responding across animals ranged from 2 to 23 responses/min, but response rates within subjects were less variable. Rats responded at an average of 95% ± 5% S.E.) of baseline after vehicle injections. All compounds tested caused a suppression of operant responding in that they decreased response rate below the criterion of 75% of baseline. Table 1 shows the calculated dose at which half the animals met the criterion for suppression (SD50) and the 95% CIs for each compound tested. Of all the compounds evaluated after i.p. administration (Fig. 2), triazolam (0.03–1.0 mg/kg, 10 min; n = 12) was the most potent and exhibited an SD50 of 0.2 mg/kg (0.1–0.4 mg/kg, 95% CI). Zolpidem (0.1–1.0 mg/kg, 30 min; n = 13) and pregnanolone (0.1–10.0 mg/kg, 30 min; n = 13) were also potent suppressants of operant responding, resulting in SD50s of 0.7 mg/kg (0.3–1.6 mg/kg) and 0.6 mg/kg (0.2–1.8 mg/kg), respectively. Pentobarbital (3.0–17.0 mg/kg, 30 min; n = 15), on the other hand, was less potent than the other GABA_A-positive modulators, with an SD50 of 6.8 mg/kg (4.9–9.5 mg/kg).

The neuroactive steroids, CCD 3693 (4.0–16.0 mg/kg; n = 19), Co 134444 (4.0–24.0 mg/kg; n = 14), Co 177843 (4.0–16.0 mg/kg, n = 11), and Co 127501 (2.5–10.0 mg/kg; n = 10) were dosed p.o. 15 min before the session and exhibited dose-
related decreases in responding. CCD 3693 exhibited an SD50 of 8.7 mg/kg (6.6–11.3 mg/kg). The novel neuroactive steroids Co 134444, Co 177843, and Co 127501 exhibited SD50s of 10.4 mg/kg (6.3–17.0 mg/kg), 6.3 mg/kg (3.8–10.5 mg/kg), and 3.9 mg/kg (2.4–6.2 mg/kg), respectively (Fig. 3). These values were compared with the SD50 of 2.4 mg/kg (1.2–4.9 mg/kg) obtained with zolpidem (1.0–10.0 mg/kg; n = 11; Fig. 3).

**Rotorod.** A subset of the compounds were evaluated for ataxia with the rotorod assay (Fig. 4). The lowest dose of each compound tested had little effect in the rotorod assay. Increasing the dose of each compound caused an increase in the number of rats failing, or falling off the rotorod. Table 1 shows the calculated TD50 and the 95% CIs of each compound. Triazolam administration (0.1–3.0 mg/kg i.p., 10 min) resulted in a TD50 of 0.5 mg/kg (0.3–0.8 mg/kg). Pentobarbital (10.0–40.0 mg/kg i.p., 15 min) exhibited a TD50 of 16.6 mg/kg (13.3–20.6 mg/kg). Co 127501 (10.0–60.0 mg/kg p.o., 60 min) and Co 134444 (10.0–60.0 mg/kg p.o., 30 min) resulted in TD50s of 30.4 mg/kg (20.4–45.3 mg/kg) and 28.3 mg/kg (21.1–37.8 mg/kg), respectively. Similarly, Co 177843 (10.0–60.0 mg/kg p.o., 60 min) exhibited a TD50 of 29.1 mg/kg (23.1–36.6 mg/kg). Zolpidem (10.0–60.0 mg/kg p.o., 30 min) exhibited a TD50 of 22.9 mg/kg (16.0–32.8 mg/kg).

**EEG.** The effects of all the test drugs on NREM and REM sleep are summarized in Table 2. Pentobarbital (10.0 and 30.0 mg/kg i.p.) significantly increased NREM sleep (F<sub>2,38</sub> = 65.13, p < .0001) and decreased REM sleep (F<sub>2,38</sub> = 9.04, p < .001). Post hoc analyses revealed that only the 30.0-mg/kg dose of pentobarbital caused an increase in NREM sleep, whereas both 10.0 and 30.0 mg/kg caused a decrease in REM. Zolpidem (5.0 and 10.0 mg/kg p.o.; F<sub>2,42</sub> = 8.26, p < .001) and the neuroactive steroids Co 134444 (8.0–18.0 mg/kg p.o.; F<sub>3,37</sub> = 9.48, p < .0001), Co 177843 (3.0–10.0 mg/kg p.o.; F<sub>3,35</sub> = 20.22, p < .0001), and Co 127501 (3.0–10.0 mg/kg p.o.; F<sub>3,42</sub> = 22.09, p < .0001) also significantly increased NREM sleep. Post hoc analyses indicated that 12.0 and 18.0 mg/kg Co 134444, but not 8.0 mg/kg, were statistically different from vehicle. Similarly, the two higher doses tested (6.0 and 10.0 mg/kg) for Co 177843 and Co 127501 increased NREM sleep, whereas the lowest dose tested of each (3.0 mg/kg) had no effect. Of the two doses tested of zolpidem, 10.0 mg/kg statistically increased NREM sleep, but the effect at 5.0 mg/kg was not statistically significant.

In contrast to the pentobarbital-induced decrease in REM sleep, zolpidem (F<sub>2,42</sub> = 1.80, p = .1778), Co 177843 (F<sub>3,35</sub> = 0.80, p = .5040), and Co 127501 (F<sub>3,42</sub> = 0.73, p = .5415) had no effect on REM sleep. Co 134444 (F<sub>3,37</sub> = 3.02, p < .05) significantly decreased REM sleep, but post hoc analyses revealed that only the high dose (18.0 mg/kg) of Co 134444 was statistically different from vehicle.

**Discussion**

The GABA<sub>A</sub>-positive allosteric modulators tested in this study produced dose-related decreases in response rates under a VI 2-min schedule of positive reinforcement, dose-related increases in ataxia, and significant increases in NREM sleep in rats. Our results are consistent with and compared with previous results reported by Edgar and colleagues (1997; Table 1). Also consistent with a previous report (Bayley et al., 1996), all of the compounds tested more potently suppressed response rates in an operant task than caused
ataxia in a rotorod assay. Furthermore, the rotorod assay was less sensitive to pharmacological manipulation than the EEG assay. In this study, the potency in the operant assay appeared to be a better predictor of soporific potency than rotorod in that all of the compounds were more potent in operant and EEG assays than they were in the rotorod assay. Thus, operant behavior may be a useful screen to narrow the number of compounds needed to be evaluated in the EEG assay.

The neuroactive steroids CCD 3693, Co 134444, Co 177843, and Co 127501 were administered orally and robustly suppressed operant responding 15 min after administration. These results are consistent with good oral bioavailability and rapid onset of pharmacological effects, two desirable qualities of a sedative-hypnotic therapeutics. These effects were similar to those observed with the clinically active sedative-hypnotic zolpidem, which also showed a rapid onset orally and suppression of operant responding. Furthermore, our experiment demonstrated that Co 134444, Co 177843, and Co 127501, as well as zolpidem, increase NREM sleep at doses that have no effect on REM sleep. In contrast, pentobarbital disrupted REM sleep at a lower dose than it increased NREM sleep. These results suggest that neuroactive steroids, like zolpidem, may increase duration of sleep without altering its natural architecture and exhibit clinical advantages over barbiturates and other hypnotics that show profound effects on REM sleep.

All of the compounds except pentobarbital showed some separation between hypnotic and ataxic effects in that they were more potent in the EEG assay than in the rotorod assay.
Pentobarbital exhibited the reverse profile, with a greater potency in the rotorod assay. Note, however, that if a dose between 10.0 and 30.0 mg/kg pentobarbital had been tested, the TD_{50} and MSD may have been more closely matched. Of all the compounds for which a definitive MSD was determined, Co 127501 and Co 177843 exhibited the largest separation, with an approximate fivefold difference between the two activities. The wide separation between soporific activity and ataxia with Co 127501 and Co 177843 suggests that these compounds may have clinical advantages over other sedative-hypnotic drugs. A compound with greater separation between hypnotic and ataxic effects in animals may produce less motor impairment at therapeutic doses in humans and thus aid in avoiding falls and other associated health problems. In fact, motor impairment associated with benzodiazepine and zolpidem use has been associated with increased frequency of falls (Mendelson and Jain, 1995; Mendelson, 1996; Neutel et al., 1996; Ebly et al., 1997). This finding is consistent with a narrower difference between rotorod TD_{50}s and EEG MSDs for triazolam (i.p.) and zolpidem (p.o.), although the MSDs are estimated based on only the doses tested, thus making definitive comparisons difficult.

Note that any drug with behavioral effects may, at some dose, disrupt operant responding, including psychomotor stimulants and other drugs without sedative-hypnotic effects. For example, psychomotor stimulants engender stereotypic behaviors, such as sniffing and grooming, at high doses that interfere with lever-pressing behavior. Suppression of operant responding in isolation is therefore not predictive of soporific efficacy. Given that suppression of operant responding was predictive of soporific potency among several positive allosteric modulators of GABA_{A} receptors, however, it may be a useful tool for sedative-hypnotic drug discovery when considered in the context of other information regarding efficacy, such as other behavioral indicators and pharmacological class. Indeed, rotorod may remain an important predictor of sedative/ataxic efficacy.

In summary, the current strategy of using operant screening to predict soporific potency in rats resulted in the identification of three novel sedative-hypnotic compounds with good oral bioavailability and a rapid onset of effect. Co 134444 increases NREM sleep at doses that produce no effect on REM sleep and exhibits a behavioral profile similar to that of the recently characterized neuroactive steroid CCD 3693 (Edgar et al., 1997). Co 134444 has the additional advantage of being soluble in aqueous media. Moreover, Co 127501 and Co 177843 increase NREM sleep at doses that produce no effect on REM sleep and exhibit a novel profile with a wide separation between soporific activity and ataxia. Such a separation may indicate a potential clinical advantage over currently available hypnotic therapeutics. The current screening strategy of operant, rotorod, and EEG assays appears to be a useful means of identifying novel sedative-hypnotic drugs with the potential of an improved side-effect profile.

Acknowledgments
We thank M. Huber, S. Robledo, and M. Suruki for excellent technical assistance and Dr. H. Xia for original synthesis of Co 134444.

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