Hypnotic Activity

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General Considerations

The term "hypnotic" has to be defined. In man, the purpose of taking hypnotics is to obtain a "normal" night's sleep from which the patient can be aroused without any subsequent hangover. In animal experiments, the term "hypnotic" has been applied to a much deeper stage of central depression of drug induced unconsciousness associated with loss of muscle tone and of righting reflexes. Therefore, most of the pharmacological models are questionable in regard to their predictivity to find an ideal hypnotic for human therapy. Many of the pharmacological tests are based on the potentiation of sleeping time induced by barbiturates or other sedative agents.

Since the biochemical events during sleep are rather unknown no in vitro method exists for testing compounds with potential hypnotic activity.

In Vivo Methods

Potentiation of Hexobarbital Sleeping Time

Purpose and Rationale

The test is used to elucidate CNS-active properties of drugs. Not only hypnotics, sedatives, and tranquilizers but also antidepressants at high doses are known to prolong hexobarbital induced sleep after a single dose of hexobarbital. The loss of righting reflex is measured as criterion for the duration of

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hexobarbital-induced sleeping time. Mice are used in this test, since metabolic elimination of hexobarbital is rapid in this species.

Procedure

Groups of 10 male NMRI-mice with an average weight of 18–22 g are used. They are dosed orally, i.p. or s.c. with the test compound or the reference standard (e.g., 3 mg/kg diazepam p.o.) or the vehicle. Thirty min after i.p. or s.c. injection or 60 min after oral dosing 60 mg/kg hexobarbital is injected intravenously. The animals are placed on their backs on a warmed (37 °C) pad and the duration of loss of the righting reflex (starting at the time of hexobarbital injection) is measured until they regain their righting reflexes. Injection of 60 mg/kg hexobarbital usually causes anesthesia for about 15 min. If there is any doubt as to the reappearance of the righting reflex, the subject is placed gently on its back again and, if it rights itself within 1 min, this time is considered as the endpoint.

Evaluation

Mean values of duration of anesthesia (min) are recorded in control and experimental groups. The percent change in duration of anesthesia is calculated in the experimental groups as compared to those of the controls. ED_{50} values can be calculated. ED_{50} is defined as the dose of drug leading to a 100 % prolongation in duration of anesthesia in 50 % of the animals.

Critical Assessment of the Method

The anxiolytic agents of the benzodiazepine type show an uniform pattern with oral ED_{50} values of less than 1 mg/kg. This is in agreement with the fact that barbiturates also show anxiolytic activity in anti-anxiety tests with animals as well as in patients. Neuroleptics, such as chlorpromazine and haloperidol, also prolong hexobarbital sleeping time in low doses. The test is considered to be unspecific since compounds which inhibit liver metabolism of hexobarbital also prolong time of anesthesia. Balazs and Grice (1963) discussed the relationship between liver necrosis, induced by CCl_4 or nitrosamines, and pentobarbital sleeping time in rats.

Other Uses of the Test

Hexobarbital sleeping time is not only prolonged by the simultaneous administration of many compounds but also shortened under special conditions. Several CNS-active compounds (analeptics and stimulants like amphetamine and related compounds and methylxanthines) reduce hexobarbital sleeping time. Standard compounds for this kind of procedure are pentylenetetrazol, methamphetamine and aminophylline.

After repeated administrations, induction of metabolic enzymes in the liver is caused by many compounds and leads to an increased destruction of hexobarbital. Due to the accelerated metabolism of hexobarbital, sleeping time is reduced (Remmer 1972).

Modifications of the Test

Instead of hexobarbital, another barbiturate, thiopental can be used which has been proven in clinical use to be a short acting anesthetic. Test compounds or the standard are given 60 min before i.v. injection of 25 mg/kg thiopental to mice with a weight between 18 and 22 g. The animals are placed on their backs and the reappearance of the righting reflex is observed. The ED_{50} which results in a 100 % prolongation in duration of anesthesia is between 2.5 and 4.0 mg/kg diazepam p.o.

Simon et al. (1982) tested the interaction of various psychotropic agents with sleep induced by barbital or pentobarbital in mice. Pentobarbital (50 mg/kg) or barbital (180 mg/kg) were injected i.p. and the latency and duration of sleep (loss of righting reflex) were recorded. The test compound was usually administered i.p. 30 min before the injection of the barbiturate. The test was recommended for detecting sedative or anti-sleep activity. Since pentobarbital is metabolized by the liver whereas barbital is not, a comparative study using the two compounds can be useful for determining whether an eventual potentiation or antagonism can be ascribed to enzymatic inhibition or induction.

Fujimori (1965) recommended the use of barbital-Na instead of hexobarbital for the sleeping time test since barbital is not biotransformed by the liver microsomal system.

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Experimental Insomnia in Rats

Purpose and Rationale

James and Piper (1978) described a method for evaluating potential hypnotic compounds in rats. Usually, the compounds are tested in normal animals where they do not significantly decrease wakefulness. Footshock induced "insomnia" in rats is proposed as suitable model for insomnia in patients.

Procedure

Male Wistar rats (200–275 g) are prepared for chronic electroencephalographic and electromyographic recordings. Four silver/silver chloride epidural electrodes and two disc nuchal electrodes are implanted. A minimum of 10 days is allowed for recovery from surgery. The animals are placed into soundattenuated recording chambers with grid floors. The frontal-occipital electroencephalogram and the electromyogram are recorded via nonrestraining recording leads on a polygraph and a tape recorder.

On the control day, the animals are dosed with the vehicle and a control nonstress recording is obtained for 8 h. On the next day, the animals are again injected with the vehicle and then exposed to electric footshocks for 8 h. The footshock is delivered through the grid floor of the recording chamber using the EMG leads as indifferent electrodes, in the form of a 0.5 mA pulse of 15 ms width for 30 s at 1 Hz. During the footshock the EEG and EMG recording circuits are automatically interrupted. The delivery of electric footshock is triggered automatically by two adjustable timers. In this way, each shock period of 30 s is followed by an interval of 30 min. On the next day the rats are dosed with the test compound or the standard and recordings are obtained during a shock session of 8 h.

Evaluation

The sleep-wake cycle is definitely altered by the stress procedure. The amounts of arousal and of slow wave sleep I are increased, whereas slow wave sleep II and paradoxical sleep are decreased. Phenobarbital and benzodiazepines antagonize these changes at least partially.

Critical Assessment of the Method

For screening procedures, the method is too expensive and time-consuming. However, the EEG-parameters in a situation of insomnia similar to men can indicate the usefulness of a new compound.

Modifications of the Method

Gardner and James (1987) described a modified shortened protocol in which a 2.5-h nonstressed control period is followed by drug or vehicle administration and a further 5.5-h recording of the electrocorticogram in the presence of intermittent footshock.

Laval et al. (1991) studied the effect of anxiolytic and hypnotic drugs on sleep circadian rhythms in the rat.

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EEG Registration in Conscious Cats

Purpose and Rationale

The effect of hypnotics on sleep pattern of EEG tracings can be studied in conscious, freely moving cats with chronically implanted electrodes (Heinemann et al. 1970, Heinemann and Stock 1973; Wallach et al. 1976; Hirotsu et al. 1988).

Procedure

Female cats weighing 2.5–3.5 kg are anesthetized and prepared with bipolar subcortical electrodes in the reticular formation (A3, L3, H −1), dorsal hippocampus (A5, L −5, H8), and either amygdala (A12, L −9, H −5), or caudate nucleus (A11, L9.5, H −2). Cortical screw electrodes are placed over the anterior suprasylvian, lateral, medial suprasylvian and ectosylvian gyri. Two Teflon coated steel wires are placed in the cervical neck muscles. All wires are connected to a subminiature socket and implanted in dental acrylic. Cats of this chronic colony are then intermittently utilized for drug experiments at interdrug intervals of at least 2 weeks.

On experimental days, the cats are taken into an experimental chamber 70 × 80 × 80 cm high. The box is lighted and ventilated with room air at 21 °C. The cat is immediately connected to a cable which exits through the top center of the cage into a mercury swivel. This prevents the cable from becoming twisted and restricting the cat's movement. Recordings of the cortical EEG, cervical neck muscle tone and reticular formation multiple unit activity are obtained. Continuous recordings for up to 96 h are amplified and stored in a recorder. The recordings of cortical EEG, cervical neck muscle tone and reticular formation multiple unit activity are analyzed for REM sleep, slow wave sleep, and wakefulness. Undefined periods which can not be identified either as slow wave sleep or as wakefulness are included in the awake total. Since a first night effect was observed (Wallach et al. 1976) drugs are given at the 3rd or 4th day.

Evaluation

The data are analyzed by analysis of variance with subjects, days, and drug as factors.

Modifications of the Method

Schallek and Kuehn (1965) measured the effects of benzodiazepines on spontaneous EEG and arousal responses in cats with implanted electrodes.

In addition to EEG and electromyogram, Holm et al. (1991) registered the electro-oculogram in conscious cats.

EEG studies in immobilized cats were performed by Ongini et al. (1982) for evaluation of a benzodiazepine hypnotic. Adult mongrel cats of both sexes were anesthetized with halothane. A tracheal cannula was inserted and artificial respiration was maintained throughout the experiment. The spinal cord was transected at C_2 level (Encephalè isolè preparation). The femoral vein was cannulated for i.v. injection of drugs. Cortical electrodes were inserted into the skull in the frontal, parietal and occipital areas. All incisions were infiltrated with mepivacaine 1 % to produce local anesthesia. The body temperature was maintained at 36.5–38.0 °C by an electrical heat pad. After recovery from surgery and anesthesia, a continuous EEG recording of 2 h was taken prior to drug administration. Test drugs were injected intravenously at various doses. Electrocortical activity was recorded using a

8-channel electroencephalograph. In addition, two electrodes were connected with an EEG-analyzer for the on-line evaluation of the EEG power spectrum. This was computed by the Fast Fourier Transform at a frequency range of 0–32 Hz. Power spectral plots averaging 30 s of electrocortical activity were derived during the experiment.

Shibata et al. (1994) administered various local anesthetics intravenously with constant rates of equipotent doses to cats with implanted electrodes until EEG seizures appeared. During slow rates of infusion, a tetraphasic sequence of changes was found.

Wetzel (1985) evaluated EEG recordings in freely moving **rats** by visual analysis for wakefulness, slow wave sleep or paradoxical sleep.

Krijzer et al. (1991) presented a subclassification of antidepressants based on the quantitative analysis of the electrocorticogram in the rat.

Sarkadi and Inczeffy (1996) described an integrated quantitative electroencephalographic system for pharmacological and toxicological research in the rat. Peak latencies and amplitudes of visual-evoked potentials, occurrence, duration, and linear excursions of photically evoked afterdischarges, activity, mobility, complexity according to Hjorth (1970), and absolute spectral powers of delta, theta, alpha, and beta frequency bands of background activity of visual cortex and frontal-visual leads were measured in freely moving rats.

Rinaldi-Carmona et al. (1929) performed temporal EEG analysis of the sleep-waking cycle in rats with implanted electrodes after administration of a 5-hydroxytryptamine$_2$ receptor antagonist.

Lozito et al. (1994) compared loss of righting with EEG changes in rats with implanted electrodes after single and multiple infusions of fentanyl analogues.

Jones and Greufe (1994) described a quantitative electroence phalographic method in **dogs**.

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Automated Rat Sleep Analysis System

Purpose and Rationale

Ruigt et al. (1989a, b, 1993) described an automated rat sleep classification system in rats which allows classification of psychotropic drugs such as potential antidepressants, antipsychotics and stimulants (Ruigt and van Proosdij 1990; de Boer and Ruigt 1995).

The system records and analyzes bioelectrical signals from several animals over extended periods of time. The analysis is based on three signals, the parietooccipital EEG, nuchal EMG and a movement indicator signal.

Procedure

Epidural screw electrodes are implanted over the parieto-occipital cortex of male rats weighing 250–300 g for the recording of EEG against a frontal electrode. Stainless-steel wire electrodes are inserted in the dorsal neck musculature for recording the electromyogram (EMG). After recovery from surgery animals are separately housed in a light- (12:12 h light–dark cycle) and temperature- (21 °C) controlled room. Twenty-nine hour EEG and EMG recordings are made in sound-attenuated Faraday cages from 32 rats simultaneously. Movements of the rats are detected as capacitative artefacts generated in an open-ended wire of the nonrestraining flat cable connecting the rats to a swivel commutator and to

amplification and A/D conversion units, which are hooked up through a data controller to a dedicated PDP-11/83 minicomputer system for online spectral EEG analysis and data compression.

Off-line sleep staging on a micro VAX is done per 2-s epoch based on 5 spectral EEG band values (1.0–3.0, 3.0–6.0, 6.0–9.0, 9.5–20.0, 20.0–45.0Hz), the integrated EMG level and the movement level. A first sleep stage assignment per epoch is done by application of a discriminant function to these epoch values. The discriminant function is derived from a discriminant analysis of visually classified representative recording segments from different sleep stages recorded during a separate calibration experiment for each rat. A moving average EEG smoothing procedure and a set of syntactic classification rules are then used to give a final sleep stage assignment to each specific EEG epoch.

Six sleep-wake stages are distinguished including 2 waking stages: (1) active waking characterized by movement, theta activity and high EMG, and (2) quiet waking without movement. Four sleep stages are discriminated: (3) quiet sleep, characterized by EEG spindles; (4) deep slow-wave sleep with prominent delta activity; (5) pre-REM sleep with spindles against a background of theta activity and low EMG, and (6) REM sleep with theta activity and low EMG.

Each experiment consists of 32 rats divided over maximally 4 groups, including various drug treatment groups (generally several doses of the same drug) and always one placebo group. Drug administration is done at the beginning of the light cycle of the rats. After each experiment 2–3 weeks are allowed for wash-out. Drug effects on sleep-waking behavior are assessed on several parameters extracted from the hypnogram, among which percentage time spent in each of the sleep stages per 30-min period and per rat. This gives for each compound a profile of changes over sleep stages and over time.

Evaluation

Sleep stage-dependent and sleep-independent parts of the EEG power spectrum are defined by a procedure originally developed by Fairchild et al. (1969, 1971, 1975). First, a normal canonical discriminant analysis is done on 4 EEG frequency bands (1–3, 3–6, 6–9, 9.5–20 Hz) from representative segments of only 3 visually classified sleep stages (quiet waking, deep sleep and REM sleep), the sleep stage being the dependent variable. This results in 2 sleep stage-dependent canonical variables covering 100 % of the variance in the data set and two residual canonical variables which are independent of sleep stage assignment. These 2 residual variables are subsequently used in a second canonical discriminant analysis in which the presence or absence of the drug is used as the dependent variable, resulting in a single canonical variable (the drug score) associated with the drug effect on the sleep stage-independent variance of the EEG spectral parameters.

Critical Assessment of the Method

According to the author's own judgment, antidepressants, antipsychotics and stimulants can be discriminated from each other and from placebo successfully from each other and from placebo by this method, whereas nootropics classified as placebo. Unfortunately, anxiolytics, hypnotics and anticonvulsants are classified poorly.

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