Independence of sleep EEG responses to GABAergic hypnotics: biological implications

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Abstract

GABAergic hypnotics are known to depress non-rapid eye movement delta and rapid eye movements and to stimulate non-rapid eye movement sigma (spindles) and beta EEG. This study addressed the question of whether the magnitudes of these effects are significantly correlated. Data were from a study in 16 normal subjects whose sleep was recorded for five nights under placebo and for three nights each under zolpidem (10 mg), triazolam (0.25 mg) and temazepam (30 mg). EEG was analyzed with both period–amplitude and power spectral (FFT) analysis. The magnitudes of the EEG and eye movement density responses were not significantly correlated for any of the three drugs. It is therefore unlikely that sleep responses to GABAergic drugs can be explained by the common cellular action (increased chloride conductance) of these drugs. We suggest that the sleep EEG responses are manifestations of complex (but consistent) interactions of excitation and inhibition in large brain systems although certain aspects of these responses (e.g. the different time courses of delta vs sigma and eye movement responses) may reflect molecular adaptations. A separate observation in this study was the strong traitlike characteristics of the sleep variables studied. These variables were highly correlated across nights of baseline sleep; in addition, individual differences in baseline sleep were significantly retained on the third night of temazepam administration. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Sleep; EEG; Computer; GABAergic effects; Intercorrelations; Reliability

1. Introduction

GABAergic hypnotics produce a characteristic set of changes in sleep electrophysiology. In the non-rapid eye movement (NREM) EEG, power spectral analysis demonstrates that benzodiazepines depress delta (0.3–3 Hz) power and increase spindle (12–15 Hz) and beta (15–23 Hz) power (Johnson et al., 1976, 1979, 1983). Period amplitude (PA) and hybrid methods of computer analysis also detect these effects (Gaillard et al., 1973; Gaillard and Aubert, 1975; Feinberg et al., 1977; Feinberg, 1989) and can, in addition, distinguish the degree to which the changes in spectral power are produced by changes in wave amplitude as opposed to wave incidence. PA analyses demonstrate that benzodiazepines suppress both the amplitude and incidence of NREM delta waves, but that the amplitude suppression is greater (Feinberg et al., 1977, 1979). In contrast, benzodiazepines do not alter the amplitude of sigma and beta waves; the stimulation of Fast-Fourier Transform (FFT) power in these bands is entirely produced by increased wave incidence (Feinberg et al., 1995b). In addition to these EEG effects, GABAergic hypnotics depress the incidence of rapid eye movements during REM sleep [eye movement density (EMD)]. The sleep EEG effects have been most extensively described for benzodiazepines but recently developed non-benzodiazepine GABAergic hypnotics (cf. Trachsel et al., 1990; Brunner et al., 1991) produce similar changes. Barbiturates reduce NREM delta (Feinberg et al., 1969) and decrease EMD (Oswald et al., 1963; Baekeand, 1967; Feinberg et al., 1969).

The robust electrophysiological sleep “signature” of GABAergic hypnotics raises the question of whether the sleep responses are independent or intercorrelated. A search of the literature revealed no previous study of
this issue, i.e. whether subjects with greater depression of NREM delta also show greater stimulation of NREM sigma and beta and whether the EEG effects are correlated with eye movement suppression. Correlated EEG effects might be expected because the dynamic patterns of delta, sigma and beta are mutually related: delta and sigma vary inversely in NREM but come together at their lowest levels in REM (Uchida et al., 1991). Delta and beta oscillate inversely across both NREM and REM sleep (Uchida et al., 1992). It is also possible that correlated drug effects might result from individual differences in pharmacodynamics (e.g. rates of absorption, metabolism and excretion) rather than from physiologic relations among the brain systems involved.

However, there are also reasons to expect that the GABAergic sleep responses should be independent. The delta EEG suppression involves strong reductions in wave amplitude but, as noted above, the sigma–beta stimulation is entirely the result of increased wave incidence. The stimulation of spindle activity occurs only during sleep whereas the stimulation of beta EEG is readily observed in waking as well as sleep. EMD suppression occurs during REM sleep and might be unrelated to effects on NREM EEG. Perhaps the most important reason to expect the sleep effects to be uncorrelated is that they show different time courses during both drug administration and withdrawal (Feinberg et al., 1969; Gaillard et al., 1973; Gaillard and Blois, 1989), an issue discussed further below. Since, none of these a priori considerations is conclusive we conducted an empirical test of this question using data from 16 young normal adult volunteers. These subjects each received placebo for five consecutive nights and clinically recommended doses of zolpidem, triazolam and temazepam for three consecutive nights. EEG was measured with both period–amplitude and power spectral analyses and EMD was measured with a new period–amplitude method that gives excellent agreement with visual ratings.

We also investigated several related issues. We tested the within-subject (across-night) reliability of the GABAergic-sensitive measures in baseline; unreliability in these measures would weaken any conclusions regarding the independence of the drug effects. Preliminary reports of the drug effects have been presented (Feinberg et al., 1995a,b) and a detailed analysis of the reliability of the delta, sigma and beta measurements in these subjects will be published (Tan et al., in press).

2. Methods

2.1. Subjects and study design

Subjects were paid volunteers who gave fully informed consent. Subjects were carefully screened for medical and psychiatric illness and sleep disorders by questionnaires and psychiatric interview. None was using any psychoactive drugs and random drug screens were performed throughout the study. There were 10 males and 6 females with ages ranging from 19 to 26 yr (mean = 20.1, S.D. = 2.5). The goal of the study was to elaborate the effects of a benzodiazepine and non-benzodiazepine GABAergic hypnotic on PA-measured sleep variables. Subjects were randomly assigned (double blind, crossover design) to four treatment arms of five nights each. On nights one to three of each arm subjects received either: placebo, zolpidem 10 mg, triazolam 0.25 mg or temazepam 30 mg; placebo was administered on the final two nights of each arm. These were the clinically recommended doses when the study was initiated. Placebo was administered on nights four and five of each arm to assess washout effects. Thus, on one five-night arm, subjects received only placebo. In the other three arms, they received active drug for three nights and placebo for the last two nights. Drug treatments were separated by four days or longer. Drugs and placebo were administered in an identical capsule one–half hour before lights out and subjects were in bed from 11:30 p.m. to 7:00 a.m. on each night of study and for the three preceding nights.

2.2. Recording methods

EEG and EOG signals were amplified and filtered with a Grass Model 78 polygraph at 0.3 Hz (high pass) and 0.1 kHz (low pass). The pre-amplifier output of the C3-A2 EEG was digitized at 200 Hz. The digitized data were analyzed by PA and FFT and saved to optical disk using PASS PLUS (Delta Software, St. Louis, MO, USA). A 3.5 Hz 200 μV sine wave provided a calibration signal to which both PA and spectral measurements were scaled.

2.3. Analyses of sleep EEG

2.3.1. PA analysis

The PA algorithms used in PASS PLUS have been published along with initial reports on their reliability and validity (Feinberg et al., 1978, 1980). EEG analysis was performed here on all visually scored, artifact-free epochs of NREM stages 2–4. Delta (0.3–3 Hz) EEG was measured by the zero (baseline) cross component of PASS PLUS. Delta integrated amplitude (IA) measured by PA is homologous with delta power measured by spectral analyses with the FFT: both IA and power are composite measures reflecting the contributions of wave amplitude and incidence. PA analysis can distinguish the contributions of changes in wave amplitude and incidence to changes in integrated amplitude and power. Delta amplitude was measured as zero-cross average sample amplitude (ASA) and incidence was measured as time in band (TIM). Since we had already found
Improves the correlation with visual counts. A 50 Hz lead was 50 Hz: essentially all eye movement potentials were recorded between the left outer canthus and mid forehead and were measured as PA zero-cross voltage (Feinberg et al., 1978). Eye movement potentials were recorded during REM sleep. The sampling rate for the EMD was 50 Hz: essentially all eye movement potentials are under 8 Hz with our recording parameters but may not cross zero voltage (Feinberg et al., 1978). Eye movement potentials were recorded during REM sleep. The sampling rate for the EMD was 50 Hz: essentially all eye movement potentials are under 8 Hz with our recording parameters but may not cross zero voltage (Feinberg et al., 1978).

3. Results

3.1. Drug effects

The repeated measures ANOVA demonstrated that the expected GABAergic hypnotic effects on PA-measured sleep variables were present at high levels of significance ($F_{3,45, \alpha=0.01} = 28.4$) as a result of a reduced average sample amplitude ($F=16.4$) and time/epoch ($F=34.5$). Sigma amplitude ($F=0.7$, $p=0.6$) and beta amplitude ($F=1.2$, $p=0.3$) were not significantly affected, but sigma and beta incidence (measured as derivative time/epoch) were both robustly increased ($F=28.2$ and $F=10.0$). Further descriptions of the drug effects will be presented elsewhere (Feinberg et al., submitted for publication).

3.2. Reliability of computer measures

We first tested the within-subject, across-night reliability of the computer measures on the baseline nights. If the drug-sensitive computer measurements were not reliable, our test for correlated drug responses would be weak. Both PA and FFT computer analysis yielded high internight correlations for delta, sigma and beta. The medians of four correlation coefficients across the five successive baseline nights (N1 vs N2, N2 vs N3, etc) for each measure are shown in Table 1. Correlations were higher for delta and sigma and somewhat lower but still substantial for beta with both PA and FFT methods. In addition to the strong correlations, the night to night variation in absolute values was small (Tan et al., in press).

2.4. Statistical analyses

A repeated measures ANOVA was performed on the main PA-measured variables to establish that GABAergic drug effects were indeed present and statistically significant. Reliability of the computer measures was evaluated by determining for each measure the correlation between successive placebo nights and finding the median of the four correlations. To determine the magnitude of the drug response on each measure, each subject’s value on each drug night was calculated as the proportion of his three-night baseline (placebo) mean. The response magnitude was the mean of these proportions for the three drug nights. To determine whether the magnitudes of the different drug responses were correlated, we computed Pearson correlation coefficients between the three-night means on each GABAergic-sensitive measure. If the drug responses were meaningfully correlated, one would expect negative correlation coefficients between delta and eye movement density (which are depressed) and sigma/beta EEG (which are stimulated) and positive correlations between sigma and beta, and between delta and eye movement density. Because of the high number of correlation coefficients computed, alpha = 0.01 was required for significance.
3.3. Intercorrelations of GABAergic drug response

3.3.1. PA measures

Table 2 shows that there were no significant (p < 0.01) correlations among the GABAergic drug responses of PA-measured delta, sigma and beta EEG for any of the three drugs. EMD depression was also uncorrelated with the EEG responses. Pearson r-values ranged from \(-0.27\) to 0.11 for zolpidem, \(-0.44\) to 0.31 for triazolam, 0.02 to 0.35 for temazepam. Thus, the PA data indicate that the magnitudes of the GABAergic drug responses on different sleep measures are not intercorrelated.

3.3.2. FFT measures

The FFT data (Table 2) agree with the PA results. They also show no significant correlations between the depression of NREM delta power and the stimulation of sigma and beta power in any of the drug conditions. FFT-measured EMD was also not correlated with the drug-induced EEG changes in FFT power. Pearson r-values ranged from \(-0.52\) to 0.50 for zolpidem, \(-0.42\) to 0.41 for triazolam, and \(-0.1\) to 0.50 for temazepam. As would be expected when conducting many correlation tests, a few of the FFT correlation coefficients approached significance (0.01 < p < 0.05). The correlation between the delta decrease and the sigma increase under zolpidem was \(r = 0.50, p = 0.05\), between delta and EMD was \(r = -0.52, p = 0.04\), and between sigma and EMD for temazepam was \(r = 0.50, p = 0.05\). However, these are surely chance effects because in each case the relationship is the opposite of what would be predicted.

Because of the way correlation coefficients are computed, a single aberrant point at the high or low end of the distribution can suggest a correlation where no relationship exists. The opposite phenomenon also occurs: aberrant points can reduce real correlations to insignificance and mask relations that are actually present. We plotted scattergrams for each relevant correlation and found no evidence that outlying points obscured any real relation.

3.4. Relation of individual differences in baseline to levels under drug

One question that arises from these data is whether the reliable individual differences in baseline EEG and EMD measures are retained under drug. We evaluated this question by computing correlation coefficients between the three-night baseline mean of each measure and its value on the third night of drug administration. We chose the third drug night because it usually showed the numerically largest drug responses (although most were not significantly greater than those on night two). Table 3 shows that subjects values under drug were significantly correlated with their baseline levels for both the EEG and EMD measures. Only the beta DTM measure of PA under temazepam and beta power under zolpidem failed to correlate significantly with the respective baseline (placebo) means. Thus, individual differences in GABAergic-sensitive sleep measures present in baseline were preserved under drug, adding to the growing evidence that these measures possess strong “trait-like” characteristics (Tan et al., in press).

### Table 1

<table>
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* The median of the four Pearson correlation coefficients is shown. \(N = 16, r = 0.623\) at \(p = 0.01\).  

# Table 2

Intercorrelations of the magnitudes of the drug responses (see text) for the GABAergic-sensitive sleep measures computed for the means of three drug nights for each drug

<table>
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<th>Z-beta</th>
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<td>1</td>
<td>-0.14</td>
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<td>1</td>
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* Z = zolpidem, H = triazolam, T = temazepam. \(N = 16, r = 0.623\) at \(p = 0.01\).
4. Discussion

These results advance our knowledge in several areas. First, we report that computer-measured NREM delta, sigma and beta EEG are highly reliable across nights with both PA and FFT analyses; more detailed reliability analyses which include measures of within-subject variation are being presented elsewhere (Tan et al., in press). The high reliability of these sleep EEG measures is more suggestive of “trait-like” than “state-like” characteristics. Computer-measured EMD during REM sleep was also reliable, corroborating a previous test of this question with visually rated eye movement (Feinberg, 1974b). The fact that our EEG and EMD computer measurements were reliable adds confidence to the validity of our test for correlated drug effects.

The absence of a significant correlation between baseline EMD and NREM delta merits comment. Delta, in addition to its hypothesized role as a homeostatic marker, has been shown experimentally to be the deepest stage of human sleep as measured by arousal threshold (Rechtschaffen et al., 1966). Less direct but strongly consistent evidence indicates that EMD is positively related to within-sleep arousal level. This evidence is summarized elsewhere (Feinberg et al., 1995a,b). Briefly, it includes the following: EMD diminishes under sleep deprivation and GABAergic drugs, conditions that depress arousal level. EMD increases across sleep as arousal threshold diminishes. EMD shows a spectacular late increase when the sleep of normal subjects is extended well beyond their habitual sleep length; in these extended hours, arousal level is extremely high as evidenced by frequent awakenings. It is important to note that several investigators have argued that these eye movement data could be explained by circadian control of eye movement density. While this alternative explanation could apply to the increase in eye movement density across sleep and in extended sleep, it would not explain the reduced eye movement density in either recovery from sleep deprivation or GABAergic-induced sleep.

Since NREM delta and EMD appear to have strong but opposite relations to arousal level, it is puzzling that they were not negatively correlated in either baseline sleep or sleep following GABAergic hypnotics. Part of the explanation may lie in the large and stable individual differences in both EMD and NREM delta. These electrophysiological “traits” may heavily involve extra cerebral factors (skull impedance, volume conduction, etc) as well as genetic variation in brain size. Such sources of variation might “wash out” correlations due to variations in within-sleep arousal levels.

The major finding of this study is that the magnitudes of the effects produced by GABAergic hypnotics on NREM delta, sigma and beta EEG are not significantly intercorrelated and also do not correlate with the magnitude of EMD depression. Both PA and FFT EEG measurement show the EEG effects to be unrelated. One caveat regarding accepting this result as conclusive is that the drug doses used here (with the exception of temazepam) were relatively low. One cannot exclude the possibility that larger drug doses that produce more pronounced effects would result in correlated changes. Arguing against this possibility is that our drug dosages were clinically recommended and also were sufficient to produce highly significant changes from baseline (Feinberg et al., 1995a,b).

We noted above that the different time courses of GABAergic effects on sleep variables imply that their sleep effects would not be correlated. These different temporal patterns merit brief elaboration because, in addition to their implications for hypnotic actions, they may be relevant to clinical phenomena, including tolerance and hypnotic-withdrawal delirium. Time course differences in GABAergic responses were first recognized between the REM–EMD suppression and the delta depression (Feinberg et al., 1969). The REM–EMD suppression has a rapid onset, shows little tendency to increase with repeated drug administration, and dissipates quickly on drug withdrawal. The delta depression has slower onset, increases with repeated drug administration, and can last for prolonged periods after withdrawal (cf. Kales et al., 1976). Hartmann and Cravens (1973) were among the first to emphasize the curious nature of this progressive delta suppression, a phenomenon that is the opposite of the more common tachyphylaxis drug response. The EMD–delta time course differences, whose importance was also emphasized in early work by Gaillard and co-authors (1973), was the basis of an early model for hypnotic-withdrawal
delirium (Feinberg et al., 1969) that is still viable. This early model is also consistent with the recent one-stimulus model of NREM–REM alternation (Feinberg and March, 1988, 1995). According to the one-stimulus model, the increased brain excitability in hypnotic withdrawal acts to convert NREM to REM sleep and might explain the extraordinarily high levels of REM and the low levels of stage 4 observed in delirium tremens (Greenberg and Pearlman, 1967; Gross and Goodenough, 1968).

The time course of the NREM delta suppression also differs from that of the sigma stimulation. As with EMD, the sigma stimulation has a more rapid onset and dissipation than the NREM delta suppression (cf. Gaillard and Blois, 1989). Further evidence that these result from different brain mechanisms is the finding (Gaillard and Blois, 1989) that the sigma but not the delta response to flunitrazepam can be blocked by the benzodiazepine receptor antagonist flumazenil. The absence of intercorrelations among GABAergic effects we find here is consistent with Gaillard and Blois’ important conclusion that “. . . the actions of flunitrazepam on normal sleep are heterosexual and apparently cannot be accounted for by a single mechanism” (p. 130).

What biological mechanisms account for the independence of GABAergic hypnotic effects on the different sleep measures? This independence seems inconsistent with the fact that these drugs share a common primary action at the cellular level: they increase neuronal inhibition by modifying the GABA–benzodiazepine receptor complex to increase effective chloride conductance. Knowledge of the effects of this basic cellular change on the interactions of complex brain systems is limited but we offer a few speculations below.

Organized sleep spindle bursts are a major EEG hallmark of human NREM sleep and their disappearance is the most reliable EEG indicator of stage REM onset. It is important to point out that neither PA nor FFT analyses selectively measure organized spindle bursts; they simply measure all waves falling into the spindle frequency band. However, Uchida et al. (1991) proposed that organized spindles normally dominate 12–15 Hz power, a proposal supported by the findings of Dijk et al. (1993) with a method using repeated filtering and a type of PA half wave analysis. It therefore seems reasonable to infer that increased FFT power in 12–15 Hz under GABAergic hypnotics is caused by an increase in organized spindle bursts. One might therefore hypothesize that, in addition to their other effects, GABAergic drugs directly stimulate sleep mechanisms, perhaps via the mechanisms proposed by Steriade and coworkers (1993).

Actions may also occur at the molecular level. Benzodiazepines induce both rapid and delayed gene-mediated changes in receptor function (Sieghart, 1995) that also differ by brain regions. Such differences offer attractive possibilities for explaining the different time courses of the sleep responses to GABAergic hypnotics. If so, sleep EEG responses might eventually be used as in vivo markers that reflect the integrated effects on large neuronal systems of benzodiazepine-induced changes in receptor function.

The effects of GABAergic hypnotics on NREM delta are of particular interest because this phase of sleep is thought to represent brain recuperative or homeostatic processes (Feinberg, 1974a; Borbely, 1982). Potentially relevant is that GABAergic hypnotics, including the non-benzodiazepine zolpidem (Gillin et al., 1996), lower cerebral metabolism. It has been hypothesized that, by virtue of this metabolic depression, GABAergic hypnotics slow sleep homeostatic processes and that this slowing reduces delta incidence (Feinberg et al., 1977). However, GABAergic drugs also reduce the amplitude of delta waves, an effect stronger than the reduction of delta incidence. Depressed neuronal metabolism might diminish the cortical cell bursting and membrane responses that produce delta waves in the Steriade model (Steriade et al., 1993). However, if GABAergic hypnotics depress delta wave amplitude by depressing neuronal metabolism, why should not sigma and beta amplitudes also be depressed? Presumably the same cortical neurons generate the amplitudes of all three EEG frequencies. Moreover, a single action on the neurophysiological mechanisms that generate EEG waves cannot easily be reconciled with the different time courses of delta amplitude depression vs. stimulation of sigma and beta incidence. It also seems to us improbable that any depression of cortical metabolism by hypnotics would be as strongly progressive as the delta depression. In summary, while it seems plausible that the metabolic effects of GABAergic hypnotics play a role in their effects on sleep electrophysiology, this role is not simple or obvious.

That GABAergic drugs stimulate beta EEG in sleep (and also in waking; Brazier and Finesinger, 1945; Patat et al., 1994) is also paradoxical. Increased fast (beta) EEG usually signifies increased arousal but GABAergic hypnotics decrease arousal. The same paradoxical response is seen in other conditions. Fast EEG usually appears at the onset of NREM sleep, when arousal level is declining. It is usually more prominent in REM sleep than in waking, although arousal level is by definition lower in REM. Beta EEG is also prominent during anesthesia induction and in delirium and is usually mixed with slow waves in these conditions. One possible unifying explanation is that the increased beta EEG in sleep, anesthesia and delirium all represent brain disinhibition caused by partial escape from higher cortical control.

Knowledge of the cellular and genetic effects of GABAergic hypnotics is vast and rapidly growing (Sieghart, 1995). Most of this information is based on the
study of single neurons or brain slices. The implications of these data for the "whole brain" effects found here are surely indirect. Perhaps the strongest conclusion suggested by the mutual independence of GABAergic effects on sleep is that, while they are induced by changes in chloride conductance at the cellular level, the sleep EEG responses are downstream effects of interacting patterns of excitation and inhibition in large brain systems.

We raise these issues because the remarkably robust GABAergic effects on sleep electrophysiology have received little experimental or theoretical attention from the wider fields of neuroscience. Even within sleep research there has been a greater focus on quantitatively minor (and clinically meaningless) differences among drugs than on the fundamentally similar qualitative changes in sleep electrophysiology produced by this chemically diverse pharmacologic class (Feinberg and Koegler, 1982). Nevertheless, elucidating the neurophysiologic mechanisms that produce these common effects might provide new clues to GABAergic hypnotic mechanisms of action. Currently available drugs are clinically invaluable but have important limitations. Understanding the actions of this drug class on brain systems — and sleep EEG effects might provide clues in this regard that cannot now be derived from cellular effects — could ultimately lead to the development of more effective hypothetics.

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