THE RETURN TO SLEEP *

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Six young adult subjects were awakened five to eight times per night from stage 2 sleep in a standardized manner for a series of at least 11 non-consecutive nights. After adaptation to the procedure, subjects received placebo, pentobarbital, or flurazepam on two random nights and caffeine on one night. The latency of the return to sleep after each awakening was measured. On placebo nights a characteristic U-shaped curve of latency as a function of time of night was found. Latencies were long shortly after sleep onset but decreased rapidly to about 50 sec before beginning an approximately linear logarithmic increase throughout the rest of the night. The drugs characteristically altered this time course. Pentobarbital decreased latencies in the first half of the night. Flurazepam decreased latencies throughout the night. Caffeine increased latencies during the first half of the night.

1. Introduction

Early measures of sleep such as threshold were criticized because of their discontinuous nature and were quickly relegated to secondary status when continuous EEG recordings were shown to be extremely sensitive (Webb and Agnew, 1969). However, the emergence of the EEG as an effective descriptor of the sleep process has contained sleep studies largely within two dimensions: relations between EEG stage of sleep and other variables (evoked potentials, thresholds) and the use of summary EEG data as indices of sleep (differences across age or clinical groups, effects of drugs, etc.).

Both of these dimensions ignore sleep as an ongoing, subtly changing process and fail to describe sleep as any more than the orderly cycling of brain rhythms. With the important addition of time as a primary factor in ongoing sleep, much additional information about the sequence of effects of other variables presumed to act within time (e.g. fatigue, drugs, stress, etc.) on normal sleep could be measured as a function of the level of the particular experimental element. A few EEG studies have attempted to approach time course effects by reporting first

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half-last half or third-of-the-night data. For example, Williams, Agnew and Webb (1964) and Agnew, Webb and Williams (1967) have shown tendencies for the amount of wakefulness during the night to increase as a function of thirds of the night. However, the study of sleep as a behavioral process demands both a more sensitive and an experimental view.

While many studies have reported wakefulness and awakenings during sleep and have even reported on different lengths of awakenings (Langford, Meddis and Pearson, 1972), the factors causing the arousal and allowing subsequent return to sleep were unknown and uncontrolled. The present study sought to examine the effects of amount of prior sleep on following sleep during a normal night by utilizing the latency of the return to sleep from carefully controlled awakenings. It further examined the sensitivity of the latency measure in detecting specific time course changes in response to two widely used hypnotics (flurazepam and pentobarbital) and caffeine.

Because the effects of sleep on latency across the entire night were to be examined, it was decided that a standardized waking procedure must utilize stage 2 sleep, because it is the only sleep stage which also spans the entire night.

2. Method

Six male subjects aged 21–23 were selected after: (1) showing evidence of normal sleep habits including an 8 h sleep length and a 23:30 bedtime in their responses on the Florida Sleep Inventory; (2) having minimal drug use of any kind; (3) producing alpha. After a laboratory adaptation period (minimum of four nights) during which subjects were awakened five to eight times per night with a standard procedure to be described, subjects were ready to begin the experiment proper.

Each subject spent seven more nights in the laboratory. These nights were spaced four to six days apart. On each night each subject reported to the laboratory at 22:00 for electrode placement. Three channels of EEG and one channel of EOG were recorded from standard placements (Agnew and Webb, 1972). Subjects were taken to their sleep room and allowed to sit in bed and read at 23:00. At 23:15 subjects received a pill. It was either placebo, pentobarbital (100 mg), flurazepam (30 mg), or caffeine (400 mg). The drugs were administered twice in a random fashion (double blind) except for caffeine, which was administered once, single blind, on either night 1 or night 7. These drugs and doses were chosen because they are commonly used in conjunction with or in close proximity to sleep and have well-defined effects on the EEG sleep distribution at the doses used. At 23:30 the subjects were told to go to sleep and the room lights were turned out.

Subjects had been instructed that they would be awakened five to eight times during each night by a ascending series of 1000 Hz tones produced by a Tracor RA Rudmose screening audiometer. Subjects were to verbally report being awake
when they heard the tone and to push a button taped into their hand each time they heard the tone. When subjects said they were awake, a small nightlight was turned on in the subject room to denote to the subject that he was to stay awake while his auditory threshold was tested. The subject was operationally defined as being awake if he had a waking EEG and when his waking auditory threshold was within 4 dB of the same value on three consecutive ascending series (interspersed with descending series) of signals from the audiometer. The waking period length was usually between 1–2 min. With the completion of the series, the night light was turned out and the period of latency determination began. The number of seconds from lights out to the first spindle or K complex was recorded along with the time of night.

An initial awakening was made 5 min after the onset of the first stage 2 period. The protocol for all other awakenings was that they must occur at least 5 min into well-defined stage 2 sleep, after at least 30 min of continuous sleep, and after at least 10 min without a body movement or muscle artifact greater than 6 sec. This protocol allowed normal cycling of sleep.

3. Results

Each night was arbitrarily split into five parts by time (0–80 min, 81–180 min, 181–280 min, 281–380 min, and 381+ min from bedtime) and all observations for each subject for each condition were averaged within each time block to get a single subject value for each time block for each condition. A total of 260 latencies were included in the 120 cells of the analysis. Six empty cells, all from the single caffeine night, were filled (but deleted from the degrees of freedom) with the closest of usually multiple observations in adjacent cells from the same subject and night.

Latency values are invariably skewed. As a result all within sleep latency values were transformed with a log transformation. The analysis of variance for that data is presented in table 1. There was a significant drug condition by time of night interaction \( F(12, 54) = 2.51, p = 0.01 \). However, because repeated measures designs may violate usual assumptions about ANOVA, variance–covariance matrices for the present latency data were constructed for both trials and drug condition effects, and (Winer, 1971) were found for each main effect. The values were 0.71 for trials and 0.91 for drug condition. Their product, \( D \times T \) indicated that the appropriate degrees of freedom for interaction were 8 and 34. With these degrees of freedom, the interaction was still significant \( (p = 0.05) \). Individual time by drug condition comparisons were made (Duncan Multiple Range Test). The log latency drug condition by time trial plot can be seen in fig. 1 for the four conditions and differences are noted in table 1.

In the placebo condition, the median initial sleep latency (at 23:30) was 7.3 min, which is marked with an 'X' in fig. 1. At time trial 1 in fig. 1, latency fell to
Table 1
Drug condition by time of night by subject ANOVA for log sleep latency after an awakening

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>Interaction $[F(8.34) = 2.51, p &lt; 0.05]$</th>
</tr>
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<tbody>
<tr>
<td>Subject</td>
<td>5</td>
<td>1.428</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>3</td>
<td>3.983</td>
<td></td>
</tr>
<tr>
<td>Subject X drug</td>
<td>15</td>
<td>0.188</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>4</td>
<td>0.693</td>
<td></td>
</tr>
<tr>
<td>Subject X time</td>
<td>20</td>
<td>0.080</td>
<td></td>
</tr>
<tr>
<td>Drug X time</td>
<td>12</td>
<td>0.201</td>
<td></td>
</tr>
<tr>
<td>3-Way</td>
<td>54</td>
<td>0.080</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug condition by time means</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (P)</td>
<td>2.30</td>
<td>1.71</td>
<td>1.88</td>
<td>2.03</td>
<td>2.28</td>
</tr>
<tr>
<td>Pentobarbital (N)</td>
<td>1.90</td>
<td>1.74</td>
<td>1.67</td>
<td>2.03</td>
<td>2.20</td>
</tr>
<tr>
<td>Flurazepam (F)</td>
<td>1.91</td>
<td>1.74</td>
<td>1.66</td>
<td>1.61</td>
<td>1.83</td>
</tr>
<tr>
<td>Caffeine (C)</td>
<td>3.00</td>
<td>2.77</td>
<td>2.24</td>
<td>2.33</td>
<td>2.55</td>
</tr>
<tr>
<td>$N = F &lt; P &lt; C$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 &gt; 3 = 4 = 5, 2 &gt; 3 = 4</td>
</tr>
<tr>
<td>$N = F = P &lt; C$</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N = F = P = C$</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$F &lt; N = P = C$</td>
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<tr>
<td>$F &lt; N &lt; C$</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$P = C$</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Differences found with the Duncan Multiple Range Test at the 0.05 level and based on 34 degrees of freedom.
about 3.3 min. Placebo latencies were shorter in time trial 2 (about 52 sec) and began a linear (logarithmic) increase throughout the rest of the sleep period.

Because the presented time course tends to peak at a time of night when the probability of stage 4 is relatively high, the placebo sleep records of each subject were examined to see which stage – 4, REM, or 2 – predominated in the 30 min prior to each arousal. An attempt was made to match arousals following periods of stage 4 to arousals following periods of REM and arousals following periods of REM to arousals following periods of stage 2 at the same times of night for each subject. It was not possible to match stage 2 with stage 4. Matches were averaged within subject. No significant difference with respect to previous predominant sleep stage could be found in latency, and no clear trends were evident.

The effect of the awakening procedure on the sleep distribution was also examined. Average sleep stage percentages for the last three of four baseline (non-drug) nights along with normative data from the same laboratory (Webb and Agnew, 1969) can be found in table 2. As can be seen from the table, the procedure resulted in a substantial increase in wake time during the night (stage 0), primarily at the expense of stage 2. There was also a small reduction in REM. However, the subjects in this experiment actually slept a few minutes more than the norm group did.

The hypnotics acted to shorten the initial latency and to slow the appearance of longer latencies in the latter part of the night. With pentobarbital, latency
<table>
<thead>
<tr>
<th>Stage</th>
<th>Present experiment</th>
<th>Webb and Agnew (1969)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>1%</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>2%</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>3%</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>4%</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>REM%</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>424</td>
<td>418</td>
</tr>
</tbody>
</table>

was decreased with respect to placebo in the first time point, but there was a rise in latency at the fourth and fifth time points. Flurazepam appeared to keep latencies short throughout the sleep period.

The effect of caffeine was initially very large and tended to remain throughout the night. Latencies were longer than after placebo at all points except the fourth and fifth.

4. Discussion

Fig. 1 suggests a certain amount of time necessary for sleep to establish itself even after EEG-defined sleep onset has occurred. However, after being established, the decay of the process across the rest of the night was strikingly linear (logarithmic) under placebo conditions. The log function is particularly interesting, because it was predicted by Fechner (1860) and perhaps found by Kohlschutter (1862) in a study of depth of sleep across the night. The increase in latency in the latter part of the night also accounts for reported increases in stage 0 across thirds of the night (Williams et al., 1964; Agnew et al., 1967) as increasing inability to resume sleep after an awakening.

The awakening procedure used in this experiment was minimally disruptive of the sleep as can be seen from the sleep stage data. Further, the median latency for a return to sleep was 105 sec on placebo night, which was slightly less than the average length of an awakening as calculated from a normative value for this age group (Williams, Karacan and Hursch, 1974). Finally, data from an independent study indicate that if the first two arousals of a night are not made that the latency of return to sleep after the first arousal (in the middle of the night) does not differ from latency after the third arousal on a normal night; that is, the arousal process did not appear to have an effect on following arousals.

The placebo latency data were extended by administration of the drugs. Laten-
cies were increased by the administration of caffeine. The caffeine effect was maximal early in the sleep period but continued for at least 4.5 h. It is not clear why a short acting stimulant should continue to act for so long except perhaps because the dose was chosen as one large enough to cause changes in all night sleep patterns or it was easier to disrupt the sleep of good sleepers than it was to make it better.

Latencies were shortened by the administration of both hypnotics. The effect of these drugs on latency appeared related to the time course of the drug. As can be seen from the figure, latencies after pentobarbital were shorter than placebo in the first and third trial, and the rise in latency in later trials probably indicated the end of drug activity. This finding is supported by the estimated average active period of pentobarbital of about 4.25 h, which is approximately where the third time trial ended and the fourth began.

Latencies after administration of flurazepam remained low throughout the night. Flurazepam has metabolites which have half-lives greater than the sleep period, but evidence from 7–8 h after drug administration in the threshold studies (Bonnet, 1977; Itil, 1976) and performance studies (Bond and Lader, 1973; Veldkamp, Straw, Metzler and Demissianos; and Roth, Kramer and Lutz, 1977) found effects on at least some tasks; but Siegler, Winston and Nodine, 1966; Bixler, Kales, Tan and Kales, 1973 did not) is mixed. Johnson, Church, Seales and Rossiter (1978) have found sleep latencies significantly shorter in a group of six poor sleepers in a test shortly after normal sleep onset after flurazepam administration, but did not find significant differences in latency after a stage 2 awakening in the middle of the night (flurazepam administration nights were compared to placebo nights). However, effects in such a number of studies imply real but marginal continuing action of the drug.

The fact that the hypnotics did not differ from the placebo at the second time point (see fig. 1) may represent a basement effect. The criterion for sleep onset in this study was the appearance of a spindle or $K$-complex. In normal stage 2 sleep these events may often be as much as 30 sec apart. Therefore it would be difficult if not impossible to measure a latency much lower than 30 sec.

The present data obviously reflect the combined effects of circadian time and prior sleep on latency to sleep onset. However, as circadian effects would predict shorter latencies across the entire sleep period (Webb and Agnew, 1975; Weitzman, Nogeire, Penow, Fukushima, Sasson, McGregor, Gallagher and Hellman, 1974; Carskadon and Dement, 1977), the actual increase in latency as a function of prior sleep might be much greater. The implication is that if subjects were shifted from 23:30 to go to bed at 9:00 (when circadian effects start to predict increases in latency), the sleep period would be much shorter and would contain

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1 The Nembutal (pentobarbital) package insert estimates the active life of a dose (100 mg) of Nembutal to be 3–6 h.
more wake time. This conclusion is upheld by shiftwork studies, which report
more state 0 and an earlier termination of the sleep period when sleep occurs
in the morning (Weitzman, Kripke, Goldmacher, McGregor and Nogeire, 1970;
Webb, Agnew and Williams, 1971; Foret and Benoit, 1974).

As a whole the data fit well with many known aspects of the sleep process
and drug effects on that process. The return to sleep from carefully placed arousals
can track a meaningful behavioral time course of variables as subtle as the passing
of sleep itself. Such latency measures appear to be applicable in a number of
situations including sleep deprivation, aging, circadian shifts, and various classes
of insomnia.

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