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ROLE OF THE SPINDLES IN THE ONSET OF SLEEP

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Indexing Words

spindles in EEG; sleep deepening; tone pips stimulation synchronous, periodic, random with spindles; K-complex and sleep spindles; data processing of sleep stages

Atsushi YAMADORI. *Role of the Spindles in the Onset of Sleep.* Kobe J. Med. Sci 17, 97-111, September 1971——It was intended to explore the functional meaning of the spindles in EEG by analysing the change of sleep deepening patterns, which were recorded from three healthy men while falling asleep. Tone pips were applied as a disturbance for sleeping. The integrated 3 c/sec component in EEG was used as a sleep depth indicator. The stages of sleep were expressed according to Loomis' criteria of sleep depth, A to E. Auditory stimulation synchronous with the spindles failed to produce any effect on the sleep deepening and on distribution of spindles. With periodic tone pips having an interval of 5 seconds, the course of sleep deepening delayed for several minutes at B stage, but when it started to deepen, it shifted to D and E stage quickly without awakening. Irregular stimulation with random tone pips sustained the sleep at C stage for 30 to 40 min, neither deepened nor awakened. The auditory stimulous applied out of phase with the spindles elicited clear K-complexes, whereas stimulation in phase with the spindles failed to produce the evoked responses in the cortex. A possible mode of function on the spindles was discussed.

INTRODUCTION

Since Loomis et al. (1935)[24] observed "many spontaneous bursts of waves of 14 c/sec frequency" on the human cerebral cortex during light phase of sleep and designated these rhythmic waves as "spindles", the spindles have been described as one of the constant and definite features of human sleep by many sleep investigator. In 1942, Morrison and Dempsey[13, 28] produced rhythmic waves on the cat cortex by electrical stimulation of several nuclei of the thalamus and identified them with the "spontaneous potentials" (spindles) of a lightly anesthetized cat or a cerveau isolé cat. Since that time many studies have been devoted to investigations of the origin and nature of "recruiting responses" and "spontaneous barbiturate spindles."[2,3, 4, 8, 11, 30, 33, 34, 35] However, these phenomena were never related to the "spon-

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taneous spindles" of Einschlafen (Kleitman, 1963)[21] or the "falling asleep stage". These spindles are a true natural phenomenon to which the original name was given. Incidentally the physiological significance of the spindles in terms of the sleep concept still remains obscure.

On the other hand, many EEG data related to human sleep pattern clearly demonstrate[12, 18, 25, 32, 37] that the onset of human sleep is a very smooth progressive process and that the first phase or cycle of sleep easily attains the deep D and E stage (Loomis' criteria of sleep depth)[25], if not disturbed during the C stage in which the spindles are predominant. When the C stage lasts longer than normal, the onset and deepening process of sleep is definitely disturbed and the subject tends to wake up. This fact strongly suggests that the spindles may represent a certain important brain mechanism inducing sleep.

The purpose of the present study was to explore the functional significance of spindles by analysing the change of sleep deepening pattern when two basically different auditory stimulation (tone pips) were applied to the subject: (1) whenever spindles appeared on the cortex of the sleeping subject, with the purpose of selective disturbance of spindles. (2) at random and without relation to spindles.

In order to attain the above mentioned purpose, a circuit for automatic processing of the EEG was designed to measure the depth of sleep by using spindles and three c/sec slow waves as the most appropriate indicator of sleep depth.[6, 22] This automatic analysis was developed because any continuous manual graphing of sleep depth by visual inspection based upon various criteria[12, 18, 25] is very unreliable, if one wants to study the falling asleep process as a pattern.

SUBJECTS AND METHODS

EEGs of thirty five afternoon naps were recorded in three young male subjects in a sound deadened experimental room. In the afternoon nap the deepest phase of sleep was easily attained after the subjects were accustomed to the environment and to the experimental situation. Hence no difference was observed between night sleep and the afternoon nap as far as the first phase of sleep was concerned.

A silver disc electrode (10 mm in diameter) was placed over the vertex and a reference electrode was attached on the right ear. The vertex was chosen as a recording site since typical electroencephalographic changes during sleep appear around this region.[7, 17]

Recordings were performed by an arrangement illustrated in Fig. 1. The EEG was recorded through an amplifier on a magnetic tape in the FM mode. In order to deliver tone pips synchronously with the subject's spindles the same EEG was also fed into a spindle filter. The center frequency of the spindle filter was adjusted each time so as to correspond to the spindle rhythm of each subject, since each tended to have a different spindle frequency ranging from 12 c/sec to 14 c/sec. The filter was so designed that the output attenuated 6 db when the passing waves shifted one cycle from the center frequency. The filtered spindles were then fed to a type 161 Tektronix pulse generator to generate square pulses of 10 msec duration. Thus, the spindles were transformed into a train of pulses and fed into a sonic stimulator which

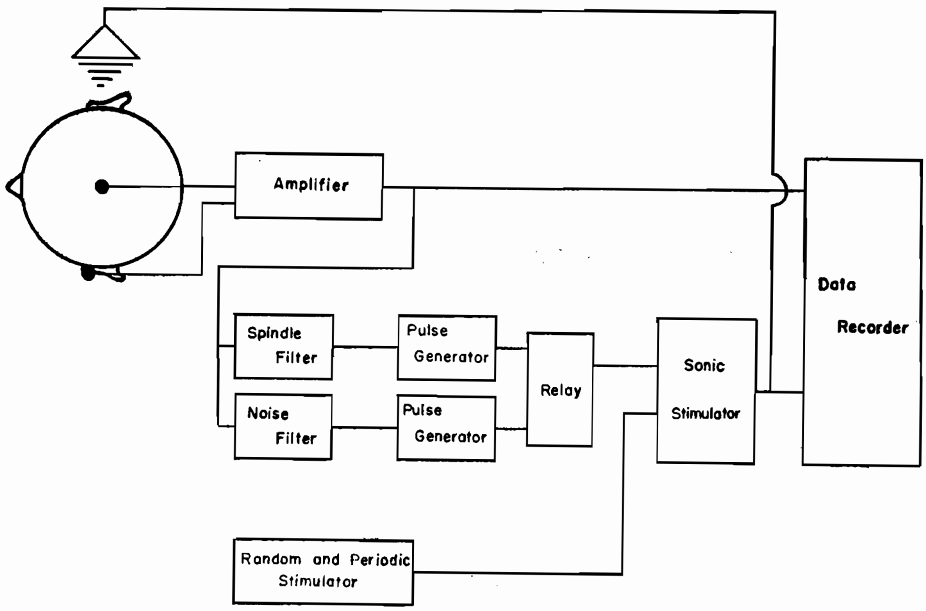

Fig. 1 Block diagram of EEG processing used in this experiment. Tone pips could be applied automatically through this circuit whenever the spindles appeared. Noises which also pass the spindle filter circuit and produce tone pips, were blocked by the relay in the noise filter circuit.

in turn produced 800 c/sec pure tone pips each having 10 msec duration. This circuit made it possible to deliver auditory stimuli automatically whenever the spindles appeared. These stimuli were also recorded on the data recorder at the same time. Because very fast components of the EEG following body movements or other origins could also pass the spindle filter like the normal spindles and trigger the sonic stimulator, a relay was put in between the pulse generator and the sonic stimulator to avoid these annoyances. The same EEG was also passed through a noise filter which eliminated waves above 90 c/sec. The output of this noise filter was then fed to another generator to produce a square wave of 2 seconds duration. Whenever noises appeared in the EEG, the relay shunted the signal to ground during this 2 seconds, preventing the pulses from the spindle filter from producing tone pips.

Two other types of auditory stimuli comprised of the same tone pips (800 c/sec, 10 msec duration) were also employed in the experiment: (1) periodic stimulation with an interval of five seconds, (2) complete random tone pips generated on a random number table. None of the stimuli were delivered before the first definite sign of sleep, at least one spindle, had appeared.[15] The effect of these two types of auditory stimulation was compared with the effect of the synchronous one.

Stimulus intensity was usually set at 30 db above threshold. Awake subjects were able to hear this tone pip without difficulty. When asleep they were never awakened by this intensity of sound.

Data processing;

Electronic analysis of sleep recording has been proposed by many investigators. Byford (1964)[9] proposed "the variance index", a ratio of any two slopes which was given by writing out the integral of the desired frequency band continuously as a function of time. In 1965, Hord et al.[20] analysed the autospectra of human sleep. Maulsby et al. (1966)[27] graphed automatically a whole sleep pattern using an integral of peak to peak voltage of rectified 2-6 c/sec frequency band as a sleep indicator. Agnew et al. (1967)[1] basing their procedure on Drohocki's method (1956),[14] plotted out minute by minute amplitude change against time.

In this present study the integrated slow waves were used as a sleep depth indicator. The graphing circuit was essentially the same as that of Maulsby although an integral of fully rectified waves was used instead of the peak to peak voltage. The 3 c/sec component was chosen as a representative of slow waves. Spindles were added as another important indicatior of the sleep stage. Fig. 2 shows an outline of the processing circuit. The first pen of a 4 channel pen-oscillograph wrote out the

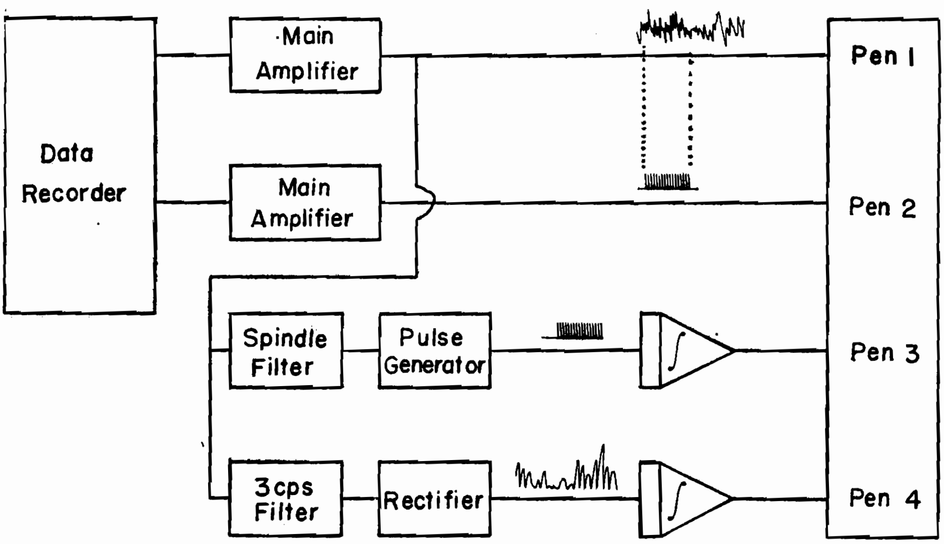

Fig. 2 Processing circuit for the EEG of sleep. Pen 1 writes out the recorded EEG. Pen 2 writes out the recorded stimulus signal. Pen 3 writes out the integral of the pulses which are generated from the spindles. Pen 4 records the integral of the 3 c/sec waves which are fully rectified.

recorded EEG at a slow speed of 0.1 mm/sec. The second pen recorded the applied tone pips. The EEG from the data recorder was also fed into the spindle filter circuit. The output pulse from this circuit was then connected to an integrator with a time constant of 10 seconds. The third pen was set to deflect upward when the integrated voltage increased, recording the "spindle amount". The output of 3 c/sec slow wave filter was fed into a full wave rectifier. The fourth pen recorded the continuous integral of these rectified waves. This integrator had the same time constant of 10 seconds. The pen moved downward as the voltage increased.

RESULTS

Sleep deepening pattern of control experiment

EEG data processing of sleep was never begun before the first definite sleep spindle had appeared on the record. At first, afternoon naps often ended in an abortive fashion; the subjects woke up during the spindle phase or fluctuated at this light level of sleep, not shifting to the deep stages, D and E in which slow waves are dominant and the spindles are very scanty.

As the subjects became accustomed to the experimental situation, their sleep

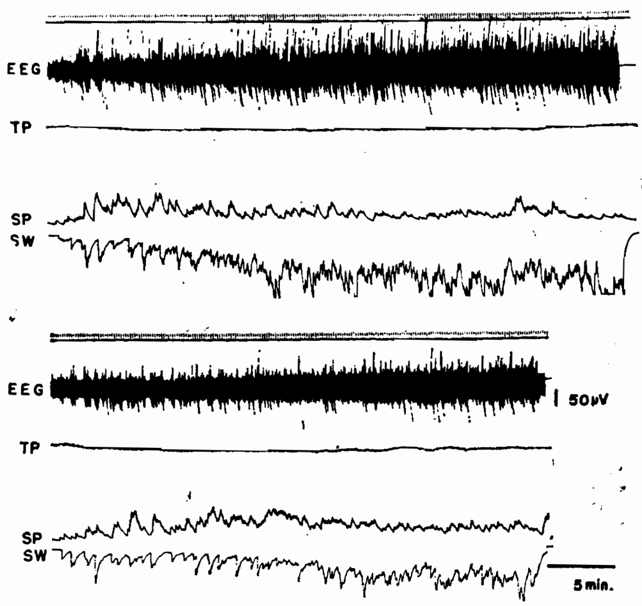

Fig. 3 Two typical patterns of normal sleep onset. Notations: EEG is the electroencephalogram of the vertex area. TP indicates tone pips applied. SP indicates the spindles and actually records an integral of the pulses having spindle frequency. SW designates the 3 c/sec slow waves and actually represents an integral of fully rectified the 3 c/sec waves; the smooth and gradual deepening process of sleep is shown in this curve.

began to have a constant pattern easily attaining to these deeper phases. Fig. 3 shows two typical patterns from different subjects. In this figure, EEG record is from the vertex area. TP indicates tone pips delivered through an auditory stimulator. No stimulus was of course applied in the control experiments. SP represents the integral of the pulses which correspond to spindles as described previously.

Consequently this curve reflects the frequency of the individual spindle and the number of spindles as a whole, and does not reflect the amplitude of an individual spindle. SW represents the integral of 3 c/sec waves which directly corresponds to the depth of sleep. From these two figures it is quite clear that sleep onset or the sleep deepening process was a fairly smooth process. The gradual deepening course of this initial phase of sleep had a duration of from about 20 minutes (upper figure) to 22 minutes (lower figure). The spindle activity was at its peak during the initial half of this downward slope. The stable plateau phase following this deepening process corresponded to the D and E stage of Loomis.[25] Throughout the control experiments this deepening course maintained a certain kind of constancy and required approximately the same time of 20 to 25 minutes before reaching the plateau phase. Furthermore this constancy and stableness was found in all subjects as well as in each individual on repeated trials. Such a constancy was not observed in the deep plateau phase of sleep. Sometimes a subject woke up ten minutes after he reached the plateau phase, sometimes the same subject tended to remain in that same phase as long as 40 minutes. The author's attention, however, was concentrated on this constant deepening process of initial sleep.

Application of synchronous stimulation

The 30 db above threshold, 800 c/sec, pure tone pips, each having a duration of 10 msec, were delivered to the subjects through the automatic processing circuit

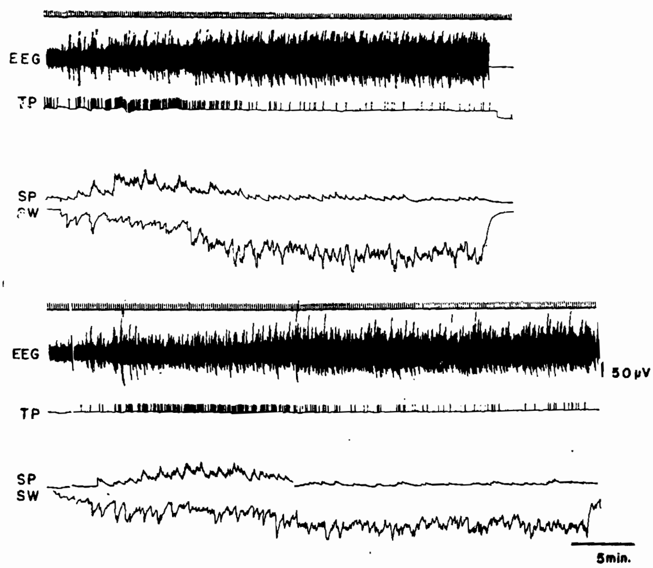

Fig. 4 Two typical patterns obtained when tone pips were applied synchronously with the spindles. No change of sleep patterns was observed. Upper records: one tone pip was delivered for one spindle burst. Lower records: a train of tone pips having the spindle frequency was delivered for each spindle burst.

whenever the spindles appeared on the cortex. Fig. 4 shows the result of the experiment. The upper figure was the pattern obtained when a single tone pip was delivered following each spindle. The subject showed no change of sleep deepening pattern as compared with the control pattern, neither did the spindle distribution change.

In the lower figure, the result is shown which was obtained when the stimulus was changed from a single tone pip to a train of tone pips. For example, when a 14 c/sec spindle appeared, 14 tone pips per second were delivered to the subject as long as the spindle continued. The amount, or the number of tone pips applied, therefore, increased very much as compared with the previous experiment. In spite of this manipulation, there appeared to be no drastic change in the deepening pattern. Although the slope of the deepening process was more gradual than in the upper record, it remained within the normal deviation, which is easy to see by comparing the record with the lower recordings in Fig. 3.

In addition to using these two modes of synchronous stimulation, the intensity of stimulus was increased by 10 db. These 40 db tone pips, again, created no change in the subject's sleep deepening pattern, although no record shown here. They were roughly the same as in Fig. 4. In all of these tests sleep reached the deep plateau phase in 20 to 25 minutes as in the control cases. The deepening slope was gradual and smooth. Spindles appeared mainly at the initial half of this slope in spite of the concentrated auditory stimulation applied in this phase. The deep stable phase which was allowed, had a duration which ranged from 10 to 45 minutes.

To sum up, the onset of sleep showed the normal pattern despite of stimulation.

Periodic stimulation

In order to compare the influence of the above mentioned synchronous stimulation with that of other types of stimulation, tone pips which were completely unrelated to the spindle appearance were used. Two modes of stimulation were employed: periodic and random. Fig. 5 shows the result of periodic stimulation at intervals of five seconds. Stimulus intensity was 30 db.

In the experiment shown in the upper record of Fig. 5, the sleep state remained rather constant for about 13 minutes after stimulus onset and then tended to deepen. The whole process of deepening took about 20 minutes. The lower figure, the result of another experiment, also showed a delay of onset of the deepening process. The initial phase of this subject's sleep remained flat for about 7 minutes. After this delay, the deepening process was initiated but in this case the subject did not stay at the deep phase and woke up suddenly. The spindle curve also shows that spindling never reached a stable low frequency of occurrence.

All other results showed one or the other of these two patterns. The deepening process was blocked and remained flat for several minutes after the stimulus onset. When this initial flat phase was over, sleep began to deepen. As for the deep plateau phase, the duration varied depending on the circumstances.

Hence, except for the first flat phase of several minutes, no constant characteristic was observed.

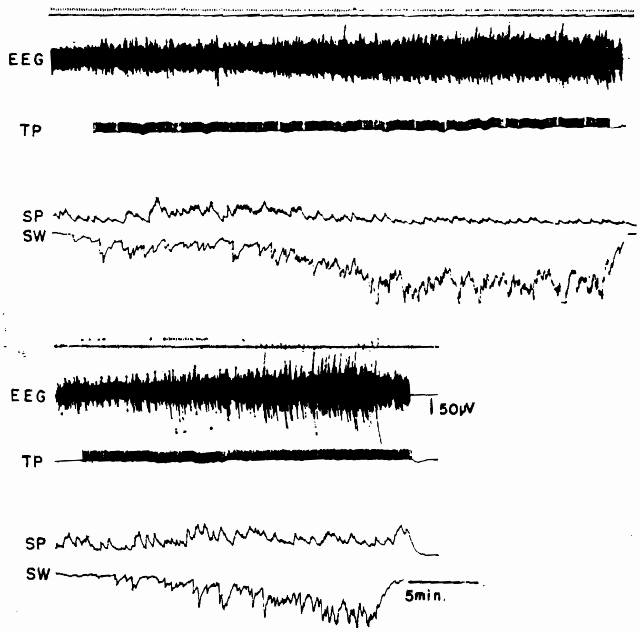

Fig. 5 Two examples of periodic stimulation. One tone pip was applied every 5 seconds. Note the initial flat phase of several minutes duration followed by gradual deepening of sleep (SW).

Random stimulation

The second mode of stimulation which was unrelated to spindle appearance was random tone pip stimulation at intervals taken from a random number table. Intensity was 30 db adove threshold. The result is shown in Fig. 6. In the upper figure, stimuli were applied as single tone pips. In the lower part of Fig. 6 is shown the result of the application of 13 tone pips per second for one second as a single stimulus. It is clearly shown that sleep never reached the deep plateau phase under both of these experimental conditions. Sometimes sleep showed a tendency to deepen but this was soon blocked and sleep remained light as shown in the lower part of Fig. 6. No difference existed between the results obtained with the single tone pip applications and with the applications of the trains of tone pips. Spindles continued to appear through out sleep, proving this to be the light phase.

Thus the random stimuli were found to be very effective in disturbing the sleep.

Response of EEG to an individual stimulus

When tone pips were applied at the spindle phase, a typical slow evoked potential called the "K-complex" appeared.[26] The left column of Fig. 7 shows

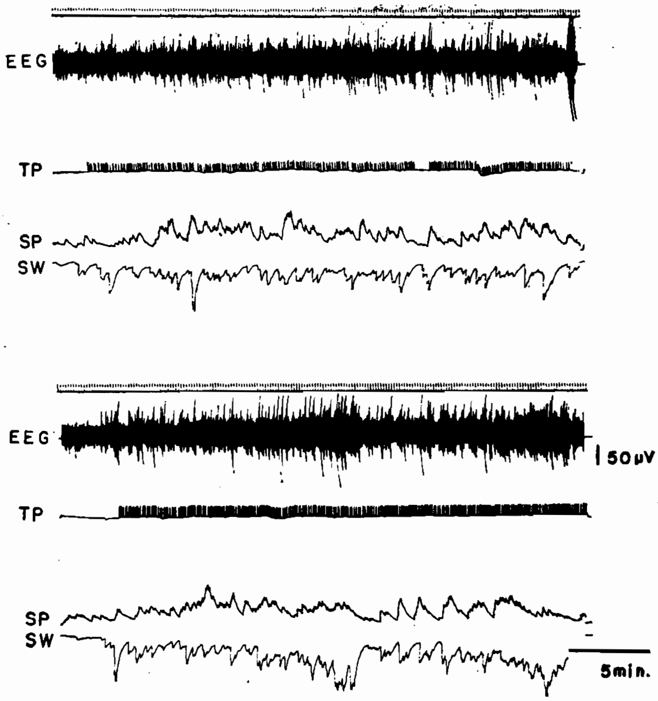

Fig. 6 Two examples of random stimulation. Upper figure: one tone pip was used as one stimulus. Lower figure: 13 tone pips/sec was used as one stimulus. Note that in both instances sleep never reached a deep phase.

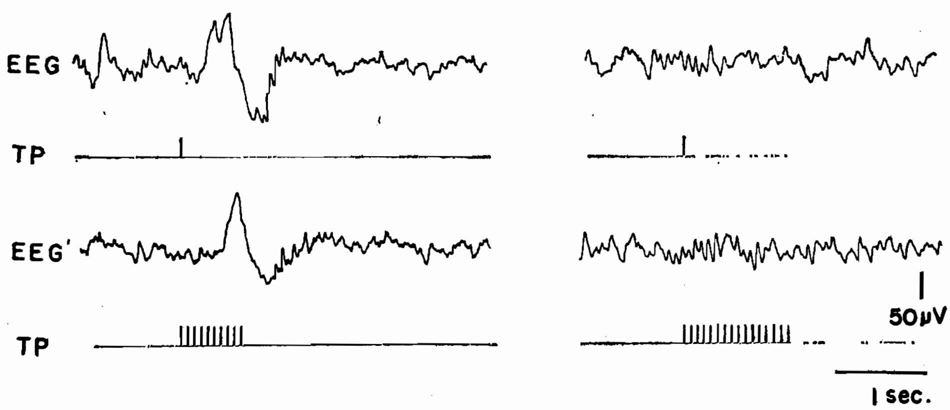

Fig. 7. Notations are the same as in the previous figures. Left column: typical K-complex elicited by stimulus out of phase with the spindle. Right column: evoked response is shown to be markedly suppressed when stimulus is synchronous with spindle. No essential difference is seen when one tone pip (upper row) or a train of tone pips issued (lower row); the spindle blocks the K-complex in both cases.

these K-complex patterns. The pattern of K-complex showed no essential difference whether it was elicited by the periodic stimulation or by the random stimulation, by a single tone pip (upper figure) or by a train of tone pips (lower figure).

However, when tone pips were applied synchronously with spindle appearance, the evoked potential was markedly suppressed (right column of Fig. 7). This effect of suppression showed no difference when a single tone pip (upper figure of right row) or a train of tone pips (lower figure of right row) was applied. No difference was observed in the various subjects studied.

The evoked response was strongly suppressed whenever tone pips were applied synchronously with spindles, whereas all the subjects responded with clear K-complexes whenever tone pips were delivered out of phase with spindles. It must be borne in mind that these typical K-complexes appeared most prominently when the subject's sleep was in its deepening phase, the C stage of Loomis in which spindles are most prominent.

DISCUSSION

The fact that the auditory stimuli applied synchronously with the spindles failed to produce any significant difference in sleep deepening pattern from the control seems to suggest that the underlying spindle producing mechanism has an active role in the sleep inducing process. This speculation is further supported by the closer examination of the EEG. The auditory evoked responses were markedly suppressed during the spindle, which indicates the sensory incoming stimuli were successfully blocked or prevented from reaching the cortex. These results suggest to the author a possible inhibitory role of the spindle producing mechanism.

In 1964, Andersen and Sears proposed that the spontaneous thalamic spindle in the lightly anesthetized cat was produced by an inhibitory mechanism in which the IPSP played an important role.[2] It was shown that the hyperpolarization occurring during the spindle markedly impaired the ability of the cell to respond with a series of regular discharges to repetitive antidromic invasion, thus indicating the inhibitory nature of the summing IPSPs, which produced the typical spindle pattern in the thalamus. In 1967, Andersen et al.[4] reported that spontaneous barbiturate spindle activity of the cat's sensory cortex interfered with orthodromic transmission through n. ventralis posterolateralis and the medial geniculate nucleus when they employed peripheral nerve volleys or clicks as a stimulus. These facts seem to coincide well with the author's present result.

Meanwhile Calvet et al. (1964)[10] reported that cortical spindle activity accompanied the bursts of discharges occurring at the level of superficial dendritic and deep units, while slow waves accompanied a suppression of the unit activity. At the level of pyramidal tract, a close correlation between the appearance of the cortical spindles and an increase in the background pyramidal tract activity was observed. The pyramidal activity fell to a minimum during the interspindle lull.[5] Hongo et al. (1963)[19] described a transient decrease in muscle spindle discharges from both the ankle flexors and extensors which occurred coincident with each EEG spindle burst in the pericruciate gyrus.

The increase of unit activity at the cortical and pyramidal tract level and the suppression of the muscle-spindle discharges during the appearance of EEG spindle, supports the view that the cortical spindle represents an active inhibitory mechanism which exerts a strong inhibition upon the peripheral musculature. The author's present results as well as those of Andersen, must be another manifestation of this same mechanism at another level. All of these facts favors an inference of Koella (1967)[23] that the sleep spindles occurring in the cortex and in subcortical structures may well be the manifestation of the particular "code" which is involved in the transfer of information pertaining to sleep, at least to slow wave sleep. However, mention must be made that the author's study was of the spindles which appear during the deepening process in natural sleep of human beings, while all the other studies referred to were of the spindles which appear under light barbiturate anesthesia in cats.

The random stimulation delivered unrelated to spindle occurrence definitely disturbed the sleep deepening process in all subjects. The periodic stimulation, when closely examined, also showed a sleep disturbing effect by delaying the deepening process for several minutes. Thus, these two modes of stimulation produced a different effect than did the spindle-synchronous stimulation; they disturbed the sleeping subject. Both modes of stimuli produced distinct K-complexes while the spindle-synchronous stimuli suppressed them. These results are in good agreement with Roth's concept that the K-complex was a crude perceptual process appropriate to a rudimentary state of awareness.[31] Oswald et al. (1962)[29] also noted that the sleeping human brain could carry out a certain kind of discrimination which was represented by the K-complex. The subjective reports in the author's experiments also support his notion. The subjects remembered the tone pips applied after awakening, while they insisted they never heard those tone pips which were applied synchronously with the spindles. This fact seems contrary to the famous opinion of Walter that the K-complex acts to muffle the arousal stimulus.[36]

It seems very probable that spindles closely correlate with a neurological mechanism which actively protects the organism from the disturbances of environment and secures the ongoing sleep deepening process.

On the other hand, the sleep inducing nature of repetitive neutral stimuli has long been known. The study by Gastaut et al. (1962)[16] clearly demonstrated this fact through the habituation of blocking of the alpha rhythm which caused the subject to fall asleep, using visual and the auditory stimulation. As for the result of periodic stimulation in this experiment, the presentation of stimuli was begun only after the subject had fallen asleep, while Gastaut's experiment was performed when the subject was awake. Further, in this experiment, the individual cortical response evoked by the individual stimulus was not systematically analysed but was studied as a whole pattern. Thus it may be incorrect to draw the reader's attention to the Gastaut's paper. The fact that light sleep was maintained without deepening for several minutes and that the deepening process was initiated after that delay "despite of" the continued stimulation means that the stimuli lost their sleep disturbing effect which they initially had. This fact could be safely explained by the same mechanism producing the phenomenon of habituation.

Random stimulation had a more definite sleep disturbing effect than did periodic stimulation. In this type of experiment, the subject never reached the deep phase of sleep, suggesting the difficulty of getting habituated to random stimuli. This fact suggests that not only the meaning of a given stimulus, a familiar name or a sound indicating danger, etc.[29], but also the temporal mode of stimulus application plays an important role in the sleeping subject's "crude perception"

SUMMARY

(1) An electronic processing circuit was designed to measure the depth of sleep, employing the 3 c/sec slow waves and the spindles as the most appropriate indicators of sleep depth.

(2) The auditory stimulation synchronous with the spindles failed to produce any differences in sleep deepening pattern from that of the control. In other words, sleep was not disturbed by this type of stimulus.

(3) When tone pips having an interval of 5 seconds were applied periodically, the course of sleep deepening was disturbed for several minutes, which appeared as an initial flat phase in the sleep deepening pattern. After this delay, sleep began to deepen.

(4) Completely random tone pips maintained the subject in a light phase of sleep. He neither woke up nor attained the deeper sleep phases.

(5) The stimuli applied out of phase with the spindles elicited clear K-complexes, whereas stimuli applied in phase with the spindles failed to produce this evoked response in the cortex.

(6) The possible inhibitory nature of the spindle producing mechanism was discussed.

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