Int. J. Neuropharmac., 1969, 8, 61–72. Pergamon Press. Printed in Gt. Britain.

DIFFERENTIAL EFFECTS OF PENTOBARBITAL, ETHYL ALCOHOL, AND CHLORPROMAZINE IN MODIFYING RETICULAR FACILITATION OF VISUALLY EVOKED RESPONSES IN THE CAT*

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(*Accepted* 5 *August* 1968)

Summary –Cortical visually evoked responses (VER) elicited by electrical stimulation of the ipsilateral optic tract were dramatically facilitated by stimulation of the midbrain reticular formation. This facilitation depended on the experimental conditions used, such as the intensity and time course of reticular (RFs) and optic tract stimulation (OTs). Reticular facilitation of the VER was most intense at 8 times the EEG activating threshold with a 50 msec interval between the RFs and OTs. The effects of increasing accumulative doses of pentobarbital, ethyl alcohol, and chlorpromazine given I.V. on reticular facilitation of the VER were observed. In general, these agents did not alter the presynaptic component of the VER except for 32 mg/kg of pentobarbital which increased it. On the other hand, pentobarbital had a marked depressant effect on both the cortical postsynaptic components and reticular influences on them. However, pentobarbital did not depress reticular facilitation of the VER as much as the non-facilitated VER. This data would suggest that pentobarbital has a neocortical depressant effect which is somewhat greater than its effect on the midbrain reticular formation. Ethyl alcohol had a similar cortical depressant effect but produced no significant depression of reticular facilitation of the VER. In fact, RFs restored the VER almost to control. Chlorpromazine (0·5 mg/kg, I.V.) reduced slightly the cortical postsynaptic components of the VER but had no effect on its facilitation by RFs.

These results suggest that reticular facilitation of the VER is more resistant to depression by pentobarbital and ethyl alcohol than the VER alone. The postsynaptic components of the VER are quite sensitive to the effects of these drugs in contrast to its presynaptic component. In marked contrast to the actions of pentobarbital and ethyl alcohol, chlorpromazine showed much less of a postsynaptic neocortical depressant effect even when massive doses (up to 16 mg/kg) were used.

IT IS WELL known from human studies that sensation is affected by spontaneous or induced alterations of consciousness. This is accompanied by obvious changes in the response of various brain structures to sensory stimuli. The reticular formation (as defined physiologically by MORUZZI and MAGOUN, 1949) has been shown to play an important role in modifying sensory patterns (CHIN *et al.*, 1965; HERNÁNDEZ-PEÓN *et al.*, 1956, 1957; KILLAM 1962; STERIADE and DEMETRESCU, 1962). CHANG (1952) showed that continuous illumination of the retina potentiated cortical responses induced by lateral geniculate stimulation. This phenomenon was investigated further by DUMONT and DELL (1958, 1960) on the visual system, and independently by BREMER and STOUPEL (1959a,b; BREMER, 1960) on the visual, auditory and somatosensory systems. These investigators clearly demonstrated reticular

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facilitation of cortical responses evoked by stimulation of the optic nerve or specific thalamic relay nuclei. In these experiments, the enhancement of centrally evoked potentials is in sharp contrast to reticular suppression of responses evoked to peripheral stimuli. Recently, facilitation of thalamic transmission by reticular stimulation has been reported by DAGNINO *et al.* (1965) and SYMMES and ANDERSON, 1967). On the other hand, it was shown by ARDUINI and HIRAO (1959, 1960) that visually evoked responses were influenced directly by retinal discharge. Thus, visually evoked responses are affected not only by the reticular formation but also by peripheral influences.

The present experiments were designed to analyze pharmacologically the role of reticular modulation of the visual system by observing the relation of altered visually evoked responses to associated reticular activity with some central nervous system depressants.

METHODS

Experiments were carried out on thirty adult cats, 2·5 4·0 kg in weight. All operative procedures were performed under diethyl ether-oxygen anesthesia administered through an intratracheal cannula. The animal was fixed in a stereotaxic instrument. The skull over the left lateral gyrus was removed and burr holes made for insertion of bipolar stimulation electrodes in the ipsilateral optic tract and reticular formation. The location of these stimulating electrodes was determined by the stereotaxic atlas of SNIDER and NIEMER (1961). The radial vein was used for drug injection. After all operative procedures were completed, the animal was immobilized with decamethonium (1–3 mg/kg per hr). All wound edges were infiltrated with 1% lidocaine repeatedly throughout the experiment to prevent pain and discomfort. Heart rate and blood pressure were monitored routinely. Respiration was maintained with an artificial respirator and body temperature kept at 36·0–37·0°C by means of a heating pad. At least 3 hr were allowed for recovery from diethyl ether anesthesia before recordings were begun.

Evoked responses were recorded monopolarly from the primary visual cortex (left lateral gyrus) with a silver ball tipped electrode. Single electrical pulses (0·03–0·05 msec and 15 V) were applied to the left optic tract (A11, L7, H-4). The indifferent electrode was placed on the occipital skull in the midline overlying the cerebellum. Electrical stimulation of the mesencephalic reticular formation (A2.0, L3.0, H1.0) usually was a 40 msec train of monophasic pulses, 1·0 msec duration and 200 Hz. The threshold for reticular EEG activation was determined for a 6 sec stimulus, 1 msec duration and 200 Hz. For examination of reticular facilitation of the VER, increasing intensities of 1, 2, 4, 8, 16 and 32 times above the threshold for EEG activation were used. Stimulating electrodes consisted of bipolar concentric stainless steel wires insulated with Araldite cement (Ciba) except at the tips. The distance of both bared tips was approximately 1 mm. EEG monitoring was carried out simultaneously on the left anterior and posterior sigmoid gyri by phonograph needles inserted into the skull and in the right hippocampus with a bipolar concentric electrode. The Grass Model III EEG was used. Evoked responses were amplified with a Grass P5 A-C preamplifier and monitored on a Tektronix Type 502 dual-beam oscilloscope. Potentials were recorded on Kodak plus-X black and white safety film by a Grass Model C4G long-recording camera automatically triggered at 5-sec intervals by a Hunter timer, which also triggered two Grass stimulators and the oscilloscope simultaneously. The peak to peak amplitude of some components of the evoked potentials was measured and the mean ± S.E. determined for each series of ten potentials.

The effects of pentobarbital, ethyl alcohol, and chlorpromazine on the VER before and after facilitation by reticular stimulation were observed. All drugs were given i.v. in a 1·0 ml volume accumulatively in doses which increased logarithmically at 10 min intervals. Recording of the evoked potentials was started 5 min after each injection. Ethyl alcohol was injected in a 25% concentration in saline. At the end of the critical experiments, a 30 sec 6 V direct current was applied to each electrode for iron ion deposition. The brain of each animal was perfused with potassium-ferrocyanide formalin solution and histological examination was performed.

RESULTS

Typical components of the visually evoked response to optic tract stimulation

The cortical VER to a single volley from the optic tract of the cat has been shown to consist of three to five successive spikes which are widely distributed over the lateral gyrus and association areas (BISHOP and O'LEARY, 1938; BISHOP and CLARE, 1952; CHANG and KAADA, 1950). The VER in the primary visual cortex elicited by stimulation of the ipsilateral optic tract (OTs) is illustrated in Fig. 1. It consists of four surface positive components (P_1, P_2, P_3, and P_4) and a long-lasting negative potential (N_4) following P_4. The

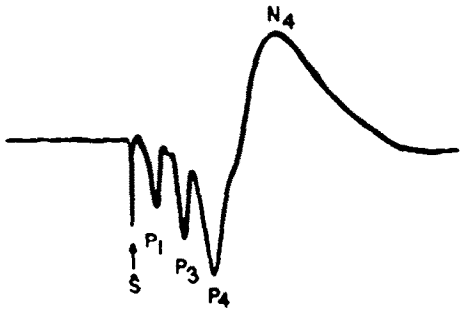

FIG. 1. Typical cortical visually evoked responses following ipsilateral optic tract stimulation. The optic tract was stimulated beyond the optic chiasm with single square wave pulses of 0·03 msec, 15 V intensity (usually 3 times threshold). Negativity in this and Fig. 4 is upward. The S represents the shock artifact. Note that the wave P_2 is barely perceptible between P_1 and P_3 and therefore was not designated.

second component (P_2) is usually very small or absent. It is known that the first wave (P_1 ·0·7–1·1 msec latency) represents the arrival of the radiation volley and is presynaptic. Waves P_4 (3·3–3·8 msec latency) and N_4 represent the post-synaptic activity of cortical cells. It is still questionable whether P_2 and P_3 represent presynaptic activity of radiation fibers or post-synaptic events. Figure 2 shows the effects of increasing intensity of 40 msec trains of reticular stimuli (RFs) on some components of the VER. Stimulation of the reticular formation started at 50 msec before the test stimulus (OTs). The ordinate shows the mean ± S.E. percent change from control and the abscissa logarithmically increasing stimulus intensities above the reticular activating threshold. All components of the potential increased

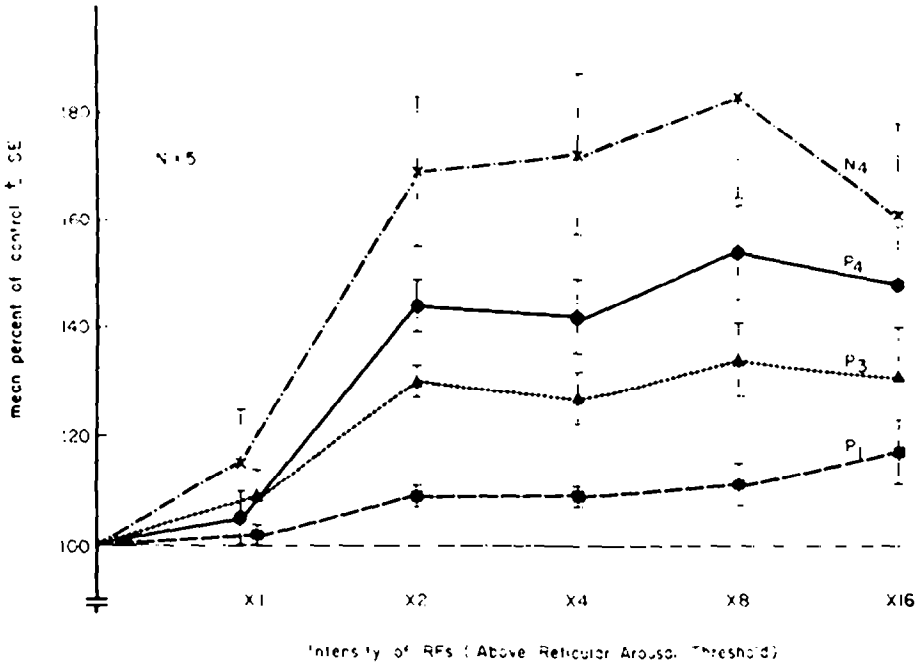

FIG. 2. Effect of reticular stimulation on some components of the VER. The effects of increasing intensity of reticular stimulation on the mean change in amplitude of various components of the VER recorded from the posterior lateral gyrus are illustrated. The parameters of stimulation of the reticular formation (RFs) were 40 msec trains of square wave pulses 200 Hz, 1 msec in duration, at 1–16 times threshold. This was followed 10 msec later by optic stimulation (OTs) with single shocks of 0.03 msec 15 V. N = five cats. The mean ± S.E. change in amplitude from control levels before and after reticular stimulation are illustrated. Note that P_1, the presynaptic cortical component, is only slightly facilitated following increasing intensities of RFs in contrast to the postsynaptic (P_4, N_4) components.

in amplitude by RFs, especially the postsynaptic components (P_4 and N_4). However, N_4 was much more variable as illustrated by the larger S.E.'s. The enhancement of the VER by RFs progressed with increasing intensity up to 8 times the EEG activating threshold. However, by using RFs greater than 8 times above threshold, the facilitatory effect on the VER was reduced except for the P_1 component (see Fig. 2). In three cats where 32 times above threshold RFs were used, all components were reduced. RFs of 4 or 8 times threshold produced typical EEG desynchronization for 1 or 2 sec after stimulation. Even in animals which showed EEG desynchronization before RFs, the VER was also markedly facilitated by RFs. This reticular facilitatory effect on the VER was strongly modified by the time course of the conditioning (RFs) and test (OTs) stimuli. Facilitation of some components of the VER was maximal at a 50 msec interval, gradually decreasing with increasing time intervals as illustrated in Fig. 3. RFs was almost ineffective at a 400 msec interval. The most striking reticular facilitatory effect on the VER was obtained with a 40 msec train of reticular stimulation 50 msec prior to the test stimulus to the optic tract with an intensity of 8 times above the EEG activating threshold. Therefore, the subsequent drug studies were carried out using these experimental conditions.

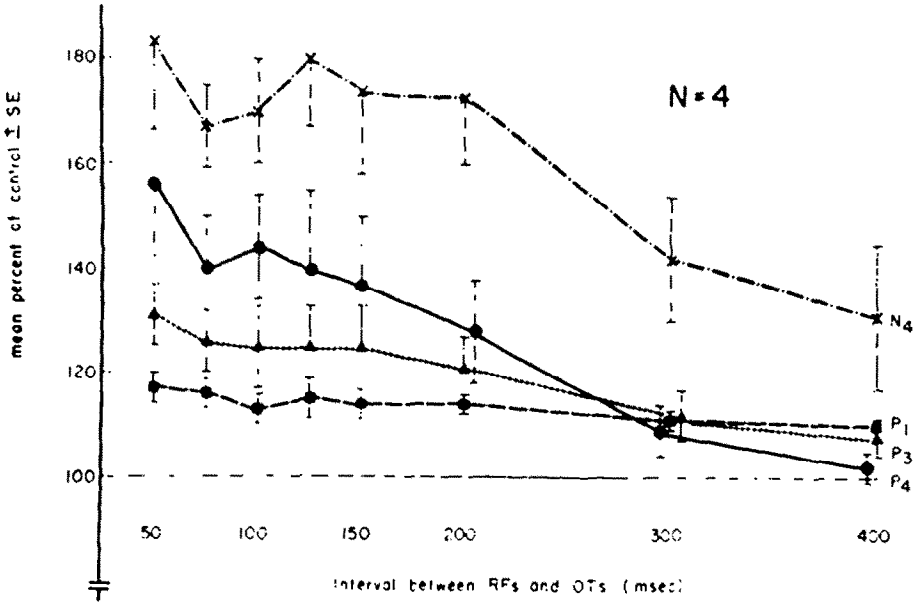

FIG. 3. Time course of reticular facilitation of the VER. The intervals from the beginning of the 40 msec train of RFs to the onset of single shocks to the optic tract are plotted on the X axis. The mean ± S.E. percent change in amplitude are plotted on the Y axis. N four cats. Note that the reticular facilitation gradually diminishes after 400 msec.

Effects of various central depressants on the reticular facilitation of the VER

To clarify the results obtained, typical evoked potentials before (no RFs) and after (RFs) reticular stimulation are illustrated in Fig. 4 for increasing accumulative doses of pentobarbital, ethyl alcohol, and chlorpromazine given to three different cats. The results obtained will be discussed separately for each drug studied.

A. *Effects of pentobarbital.* The effects of increasing doses of pentobarbital on the mean ± S.E. percent amplitude of various components of the VER for six animals is illustrated in Fig. 5. The data in panel A show the change in the mean percent amplitude from control, and the data in panel B the mean ratio of the amplitudes before and after reticular stimulation. It is helpful to compare the mean data in Fig. 5 with the individual records of Fig. 4 to follow the effects of pentobarbital. The presynaptic component (P_1) before RFs was not affected by up to 16 mg/kg of pentobarbital. As can be noted, RFs also had negligible effects on this component and pentobarbital (up to 16 mg/kg) likewise had no significant effect. In marked contrast to its ineffectiveness in altering the presynaptic cortical response, pentobarbital had a marked depressant effect on the postsynaptic component (P_4) before and after RFs. Up to 16 mg/kg pentobarbital reduced this cortical postsynaptic component to 50% of control (see Fig. 5A). Reticular stimulation was still effective in enhancing wave P_4, but less than before pentobarbital. On the basis of the ratio of amplitudes with and without RFs, reticular facilitation was actually enhanced up to 8 mg/kg of pentobarbital and subsequently reduced as noted in panel B, Fig. 5. Similar findings were observed for N_4 and to a less extent for P_3. Again in marked contrast, the presynaptic component P_1 showed no significant change of the ratio of amplitude with and without

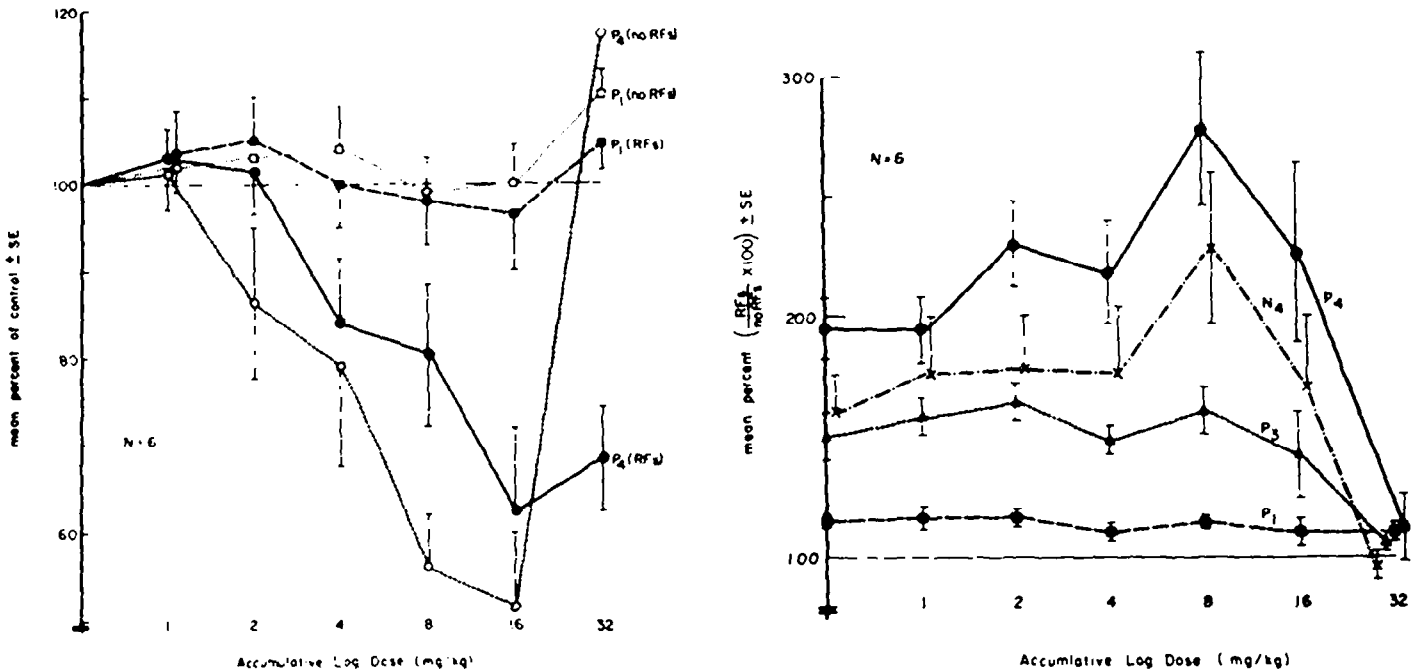

FIG. 5. The effect of pentobarbital on the VER with and without reticular stimulation. The mean change ± S.E. in the cortical presynaptic (P_1) and postsynaptic (P_4) components of the VER are illustrated in left hand graph (A) following increasing doses of pentobarbital. The mean data should be compared with the actual records from a single animal as illustrated in Fig. 4. Note that pentobarbital affects the postsynaptic component (P_4) more dramatically than the presynaptic component (P_1). In the right hand graph (B) are illustrated the differential effect of pentobarbital on the ratio of reticular facilitated/nonfacilitated pre- and postsynaptic components of the VER. The X axis represents the accumulative log dose of pentobarbital, and the Y axis the mean percent change in the amplitude of a given component of the VER with and without reticular stimulation. Note that pentobarbital has no significant effect on the presynaptic component (P_1) over a wide range of dosage. Reticular facilitation of the postsynaptic components is still evident until an anesthetic dose (32 mg/kg) is given. A paradoxical enhancement of reticular facilitation is evident in the postsynaptic components (P_4, N_4) in doses of 2–16 mg/kg.

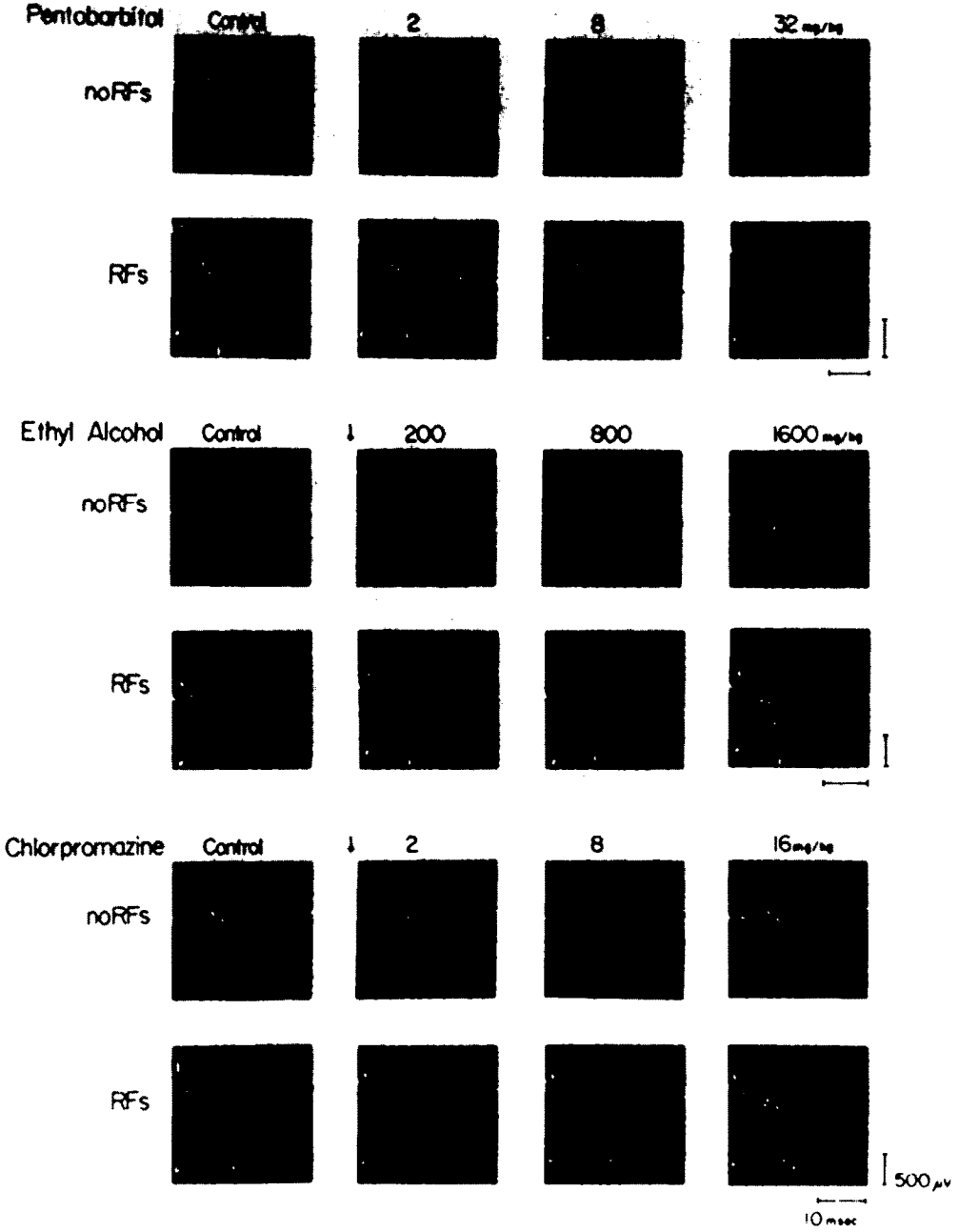

FIG. 4. Modification of the VER before and after reticular stimulation by increasing doses of pentobarbital, ethyl alcohol, and chlorpromazine. Note that subanesthetic doses of pentobarbital reduce the VER before and after reticular stimulation. Surprisingly, however, following anesthetic doses of pentobarbital (32 mg kg), the VER is enhanced rather than reduced further. In contrast, increasing doses of ethyl alcohol depress the non-facilitated VER. Reticular facilitation of the VER still occurs after a large dose of ethyl alcohol although the N_1 component is reduced from control levels. Chlorpromazine in a wide range of dosage did not alter the VER before reticular stimulation. Following reticular stimulation, a slight reduction was observed which was not further depressed even after massive doses. Calibration bars are as shown.

RFs up to 32 mg/kg of pentobarbital. However, with this large dose of pentobarbital, P_1 was enhanced above control (see Fig. 5A). A most striking finding was that at a dose of 32 mg/kg of pentobarbital, P_4 without RFs showed a dramatic increase in amplitude above that of control despite flattening the backgound EEG. In view of the fact that bilateral enucleation of the eyeballs results in a dramatic enhancement of the VER to optic tract stimulation (ARDUINI and HIRAO, 1960; HANSEN *et al.*, 1967; SUZUKI, 1967), it seemed plausible that pentobarbital in anesthetic doses was suppressing tonic retinal inhibitory discharge. Therefore, similar experiments were conducted in five animals with bilateral enucleation. Although reticular facilitation of the VER of enucleated cats was observed, it was mostly depressed after administration of more than 4 mg/kg of pentobarbital. Furthermore, there was no difference in the effect of pentobarbital upon the cortical VER with and without RFs up to 32 mg/kg of the drug. Such large anesthetic doses of pentobarbital only further depressed the VER of these bilaterally enucleated animals.

B. *Effects of ethyl alcohol.* The actions of ethyl alcohol up to 1600 mg/kg, i.v. were somewhat similar to those of pentobarbital up to 16 mg/kg. As shown in Figs. 4 and 6, the presynaptic component P_1 was not affected, while the postsynaptic component P_4 without RFs was markedly reduced to about 50% of control. However, in contrast to pentobarbital, RFs was still quite effective in facilitating this component. On a ratio basis (see Fig. 6B) the postsynaptic components P_4 and N_4 were actually enhanced after reticular stimulation. This enhancement on an absolute basis is about the same as before alcohol (see Fig. 4). In contrast to pentobarbital, ethyl alcohol did not enhance the VER in anesthetic doses as large as 3200 mg/kg, i.v.

C. *Effects of chlorpromazine.* In contrast to pentobarbital and ethyl alcohol, chlorpromazine even in massive doses of 16 mg/kg produced a much smaller depression of the postsynaptic cortical component P_4 (to 80% of control as opposed to 50% for pentobarbital and ethyl alcohol). Furthermore, the degree of depression after 16 mg/kg was no greater than that after 0·5 mg/kg. Small doses of chlorpromazine (0·5–2·0 mg/kg) caused a moderate depression in P_4 with and without RFs. No consistent significant depression of the presynaptic component P_1 was observed. The reticular facilitatory effect on the VER (as the ratio of amplitude of the responses with and without RFs) showed almost no change between 0 and 16 mg/kg of chlorpromazine in both the pre- and postsynaptic components (Fig. 7B). In other words, although chlorpromazine slightly depressed the VER by OTs, it did not depress the reticular facilitatory effect on the VER.

DISCUSSION

Since the discovery of the reticular activating system in the brainstem by MORUZZI and MAGOUN (1949), it has been demonstrated that it causes both facilitation and inhibition of sensory evoked responses (HERNÁNDEZ-PEÓN *et al.*, 1956, 1957; HERNÁNDEZ PEÓN and STERMAN, 1966; STERIADE and DEMETRESCU, 1962; TAKAORI *et al.*, 1966; CHIN *et al.*, 1965). Our findings, showing a marked reticular facilitatory effect on visually evoked responses by optic tract stimulation, confirm the previous work of BREMER and STOUPEL (1959a,b), BREMER (1960), and DUMONT and DELL (1958, 1960). It should be pointed out that there are some differences in the effects of reticular modulation of the visual, auditory, and somatosensory systems. Usually, reticular stimulation causes facilitation of visual cortical responses. However, in the auditory or somatosensory systems, the cortical responses to

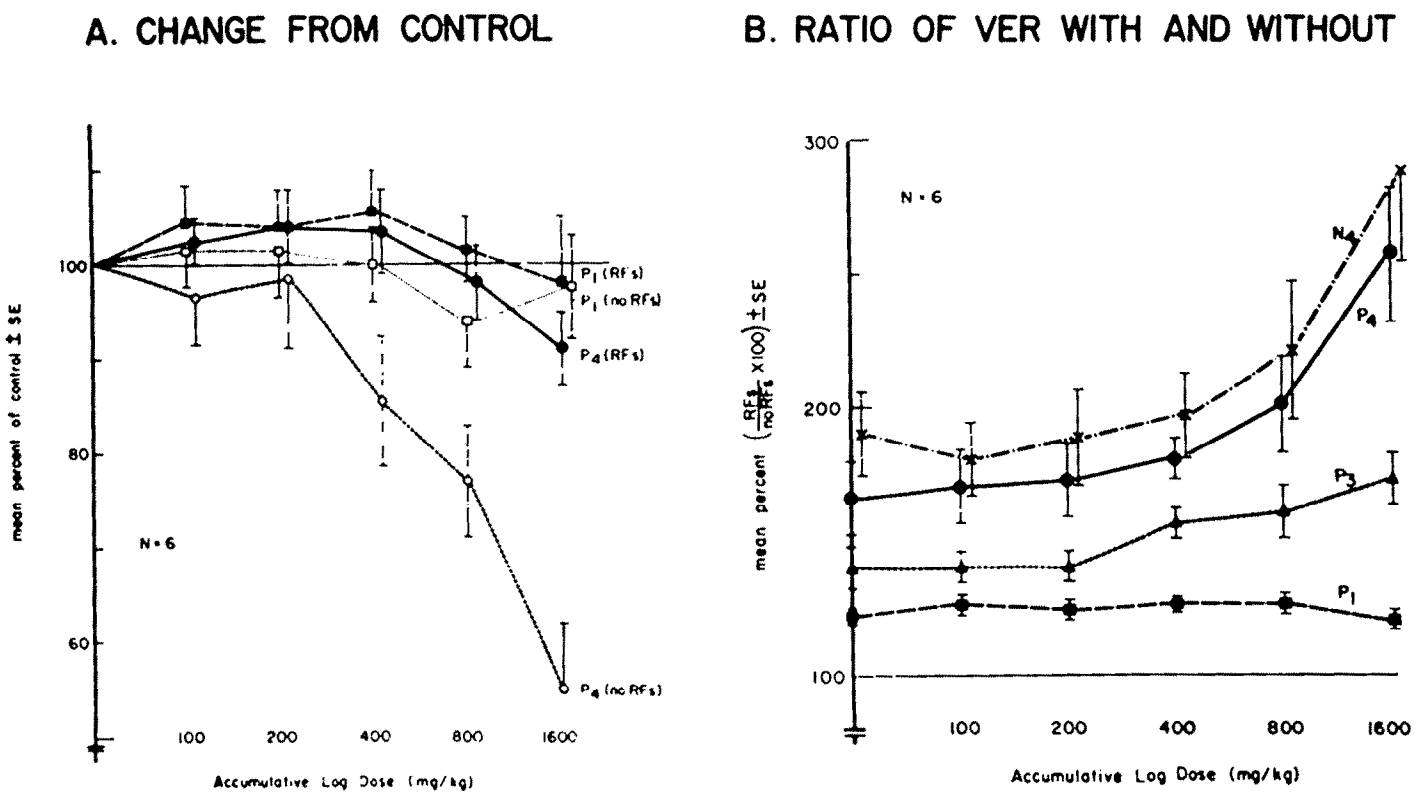

FIG. 6. Effect of ethyl alcohol on the VER with and without reticular stimulation. In the left hand graph (A) the mean change ± S.E. in the cortical presynaptic (P_1) and postsynaptic (P_4) components of the VER are illustrated following increasing doses of ethyl alcohol. The mean data should be compared with the actual records from a single animal as illustrated in Fig. 4. Note that ethyl alcohol in increasing doses progressively reduced the postsynaptic component P_4. However, reticular facilitation of this response was restored toward control levels indicating that ethyl alcohol has a greater depressant effect on the cerebral cortex which can be overcome by reticular stimulation. In the right hand graph (B) are illustrated the differential effects of ethyl alcohol on the ratio of reticular facilitated to non-reticular facilitated pre- and postsynaptic components of the VER. Note that ethyl alcohol had no significant effect on the presynaptic component (P_1). Interestingly, the postsynaptic components (P_4, N_4) following reticular facilitation are still quite evident, indicating that ethyl alcohol has a greater depressant effect on the cerebral cortex than on the reticular formation.

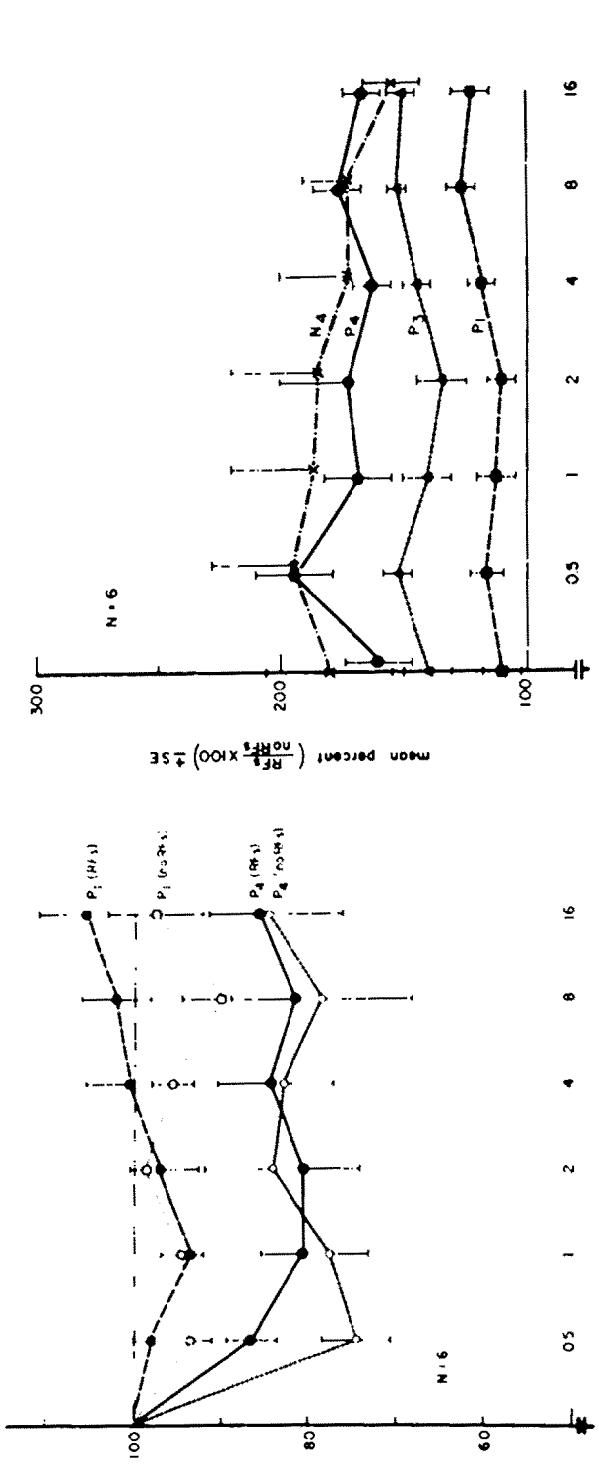

Fig. 7. The effect of chlorpromazine on the VER with and without reticular stimulation. In the left hand graph (A) the mean change ± S.E. in the cortical presynaptic (P_1) and postsynaptic (P_4) components of the VER are illustrated following increasing doses of chlorpromazine. The mean data should be compared with the records from a single animal as illustrated in Fig. 4. Note that chlorpromazine has no significant effect on the presynaptic component (P_1). The postsynaptic component (P_4) was maximally depressed in a dose of 0·5 mg kg. Reticular facilitation of this response also appeared to be depressed. Larger doses of chlorpromazine were no more effective. In the right hand graph (B) is illustrated the lack of significant depressant effects of chlorpromazine on the ratio of reticular facilitated to non-reticular facilitated pre- and postsynaptic components of the VER. In marked contrast to the depressant effects of pentobarbital and ethyl alcohol, chlorpromazine showed no significant depressant actions. Similarly, the ratio of reticular facilitated to non-facilitated pre- and postsynaptic components was not significantly altered.

reticular modulation are more variable. GAUTHIER *et al.* (1956) reported that primary responses, evoked in the somatosensory cortex by stimulation of thalamic nuclei, were not affected by either sensory or reticular stimulation.

STERIADE and DEMETRESCU (1962) have shown that there are facilitatory as well as inhibitory effects in different areas of the auditory cortex following the same reticular stimulation. Thus, reticular modulation of sensory input may be excitatory or inhibitory depending upon the recording and stimulating sites in the sensory pathway as well as the stimulating sites in the reticular formation. Despite the known variability of the effects of reticular stimuli in altering evoked responses in sensory cortex, we were usually able to observe obvious reticular facilitation in the visual cortex. As pointed out by LONG (1959), these differential effects on afferent transmission in the sensory systems may be related to a variety of anatomical and physiological differences. An especially critical point is the fact that when sensory stimulation is elicited via peripheral receptors, the effect of reticular activation on evoked responses in the corresponding neocortical sensory areas is inhibition (BREMER and STOUPEL, 1959b; HERNÁNDEZ-PEÓN *et al.*, 1956, 1957; HERNÁNDEZ-PEÓN and STERMAN, 1966). Our own observations support this general conclusion except that facilitatory as well as inhibitory phenomenon can be observed by reticular stimulation depending upon the time course of the conditioning and test stimuli as emphasized by CAVAGGIONI *et al.* (1966). DAGNINO *et al.* (1965) have suggested that during reticular activation facilitation occurs primarily at the thalamic level. SYMMES and ANDERSON (1967) have suggested that, in the monkey, facilitation also occurs primarily at the thalamic level inasmuch as they were not able to observe any reticular facilitation of auditory cortical responses by electric shocks of the thalamic radiation. However, in some of our experiments, facilitation of visual cortical responses by stimulation of the optic radiation fibers was observed following reticular activation.

It has been widely accepted that central nervous system depressants markedly affect polysynaptic structures, such as the brainstem reticular formation. This is especially true of general anesthetics and other coma-producing agents like pentobarbital and ethyl alcohol (ARDUINI and ARDUINI, 1954; FRENCH *et al.*, 1953; KILLAM, 1962). Little data is available comparing the differential effects of these agents on the reticular formation and primary sensory cortical areas. However, it has usually been demonstrated that these agents depress the reticular formation more than the primary sensory receiving areas of the neocortex (ARDUINI and ARDUINI, 1954; FRENCH *et al.*, 1953). In the present study, the effects of pentobarbital, ethyl alcohol, and chlorpromazine on the reticular formation were observed indirectly by studying reticular facilitation of the visually evoked response. By administration of pentobarbital up to 16 mg/kg and ethyl alcohol to 1600 mg/kg, i.v., the visually evoked responses without reticular stimulation were progressively depressed while the facilitated responses to reticular stimulation were only slightly depressed. Pentobarbital had the greatest depressant effect on both visual cortical postsynaptic responses and reticular facilitatory influences. Ethyl alcohol had a similar neocortical depressant effect but produced much less depression of reticular facilitation of the VER. Chlorpromazine reduced slightly the cortical postsynaptic responses but did not depress their facilitation by reticular stimulation. The latter findings with chlorpromazine are in agreement with the observations of BRADLEY and KEY (1958); although chlorpromazine depresses sensory influences elicited from the peripheral stimuli with a slight elevation of the threshold for sensory induced EEG activation, it has little effect on EEG activation produced by direct stimulation of the brainstem reticular formation.

The differential effects of pentobarbital, ethyl alcohol, and chlorpromazine on various functions of the brainstem reticular formation may be expected on the basis of the anatomical complexity of this area of the brain. With regard to the ascending pathways of the reticular formation to the cerebral cortex, many different types of neurons were observed by SCHEIBEL and SCHEIBEL (1958). One pathway to the cerebral cortex involves a series of links of short axon cells. The cells conduct at slow rates. It is logical that this system might be more sensitive to depressant effects by central nervous system depressants as exemplified by the relative ease of these agents to block EEG activation. Another important type of ascending reticular pathway involves single axon cells which originate in the brainstem and send fibers to the diencephalon. A large number of neurons of the reticular formation belong to this type. It may be expected that the central nervous system depressants have relatively little effect on these monosynaptic neurons. It may very well be that reticular facilitation of sensory input at the thalamic level is mediated by such long axon cells as evidenced by the relative resistance of this system to depression by pentobarbital or ethyl alcohol. Anatomical and physiological differences such as these may explain the relative lack of effect of ethyl alcohol on reticular facilitation of the VER in our experiments as opposed to the findings of HIMWICH *et al.* (1966) who believed that the reticular formation was more sensitive to depression by ethyl alcohol than the primary somatosensory cortex.

An extremely interesting and initially perplexing observation was that pentobarbital in doses up to 16 mg/kg, i.v. progressively depressed the cortical VER, but restored it toward control levels with anesthetic doses (32 mg/kg). This effect appears to be due to retinal disinhibition. It is well known that during the dark the retina exerts a tonic inhibitory influence on the central visual system (ERULKAR and FILLENZ, 1958; ARDUINI and HIRAO, 1959; POSTERNACK *et al.*, 1959; BISHOP *et al.*, 1964; SUZUKI, 1967; SUZUKI and ICHIJO, 1967). Our data, showing a purely depressant effect of large doses of pentobarbital in preparations with bilateral eyeball enucleation, provide indirect evidence for pentobarbital-induced depression of retinal centripital inhibition.

REFERENCES

ARDUINI, A. and ARDUINI, M. G. (1954). Effect of drugs and metabolic alterations on brain stem arousal mechanism. *J. Pharmac. exp. Ther.* **110**: 76–85.

ARDUINI, A. and HIRAO, T. (1959). On the mechanism of the EEG sleep patterns elicited by acute visual deafferentation. *Archs ital. Biol.* **97**: 140–155.

ARDUINI, A. and HIRAO, T. (1960). Enhancement of evoked responses in the visual system during reversible retinal inactivation. *Archs ital. Biol.* **98**: 182–205.

BISHOP, G. H. and O'LEARY, J. (1938). Potential records from the optic cortex of the cat. *J. Neurophysiol.* **1**: 391–404.

BISHOP, G. H. and CLARE, M. H. (1952). Sites of origin of electric potentials in striate cortex. *J. Neurophysiol.* **15**: 201–220.

BISHOP, P. O., LEVICK, W. R. and WILLIAMS, W. O. (1964). Statistical analysis of the dark discharge of lateral geniculate neurones. *J. Physiol., Lond.* **170**: 598–612.

BRADLEY, P. B. and KEY, B. J. (1958). The effect of drugs on arousal responses produced by electrical stimulation of the reticular formation of the brain. *Electroenceph. clin. Neurophysiol.* **10**: 97–110.

BREMER, F. (1960). Analyse des processus corticaux de l'éveil. *Electroenceph. clin. Neurophysiol. Suppl.* **13**: 125–136.

BREMER, F. and STOUPEL, N. (1959a). Étude pharmacologique de la facilitation des réponces corticales dans l'éveil réticulaire. *Archs int. Pharmacodyn. Thér* **122**: 234–248.

BREMER, F. and STOUPEL, N. (1959b). Facilitation et inhibition des potentiels évoqués corticaux dans l'éveil cérébral. *Archs int. Physiol.* **67**: 240–275.

CAVAGGIONI, A., GOLDSTEIN, M. H., JR. and FRIEDMAN, D. H. (1966). A further note on the time course of cortical facilitation after photic stimulation. *Archs ital. Biol.* **104**: 503–510.

CHANG, H.-T. (1952). Cortical response to stimulation of lateral geniculate body and the potentiation thereof by continuous illumination of retina. *J. Neurophysiol.* **15**: 5–26.

CHANG, H.-T. and KAADA, B. (1950). An analysis of primary response of visual cortex to optic nerve stimulation in cats. *J. Neurophysiol.* **13**: 305–318.

CHIN, J. H., KILLAM, E. K. and KILLAM, K. F. (1965). Factors affecting sensory input in the cat: modification of evoked auditory potentials by reticular formation. *Electroenceph. clin. Neurophysiol.* **18**: 567–574.

DAGNINO, N., FAVALE, E., LOEB, C. and MANFREDI, M. (1965). Sensory transmission in the geniculostriate system of the cat during natural sleep and arousal. *J. Neurophysiol.* **28**: 443–456.

DUMONT, S. and DELL, P. (1958). Facilitations spécifiques et non-spécifiques des résponses visuelles corticales. *J. Physiol., Paris* **50**: 261–264.

DUMONT, S. and DELL, P. (1960). Facilitation réticulaire des mécanismes visuels corticaux. *Electroenceph. clin. Neurophysiol.* **12**: 769–796.

ERULKAR, S. D. and FILLENZ, M. (1958). Patterns of discharge of single units of the lateral geniculate body of the cat in response to binocular stimulation. *J. Physiol., Lond.* **140**: 6P–7P.

FRENCH, J. D., VERZEANO, M. and MAGOUN, H. W. (1953). A neural basis of the anesthetic state. *Archs Neurol. Psychiat., Chicago* **69**: 519–529.

GAUTHIER, C., PARMA, M. and ZANCHETTI, A. (1956). Effect of electrocortical arousal upon development and configuration of specific evoked potentials. *Electroenceph. clin. Neurophysiol.* **8**: 237–243.

HANSEN, S. M., BRUCE, I. S. C. and BURKE, W. (1967). The effect of retinal illumination and retinal blockade on synaptic transmission in the lateral geniculate nucleus of the cat. *Vision Res.* **7**: 401–414.

HERNÁNDEZ-PEÓN, R., GUZMÁN-FLORES, C., ALCARAZ, M. and FERNÁNDEZ-GUARDIOLA, A. (1957). Sensory transmission in visual pathway during "attention" in unanesthetized cats. *Acta neurol. latinoam.* **3**: 1–8.

HERNÁNDEZ-PEÓN, R., SCHERRER, H. and VELASCO, M. (1956). Central influences on afferent conduction in the somatic and visual pathways. *Acta neurol. latinoam.* **2**: 8–22.

HERNÁNDEZ-PEÓN, R. and STERMAN, M. B. (1966). Brain functions. *Rev. Psychol.* **17**: 363–394.

HIMWICH, H. E., DIPERRI, R., DRAVID, A. and SCHWEIGERDT, A. (1966). Comparative susceptibility to alcohol of the cortical area and midbrain reticular formation of the cat. *Psychosom. Med.* **28**: 458–463.

KILLAM, E. K. (1962). Drug action on the brain-stem reticular formation. *Pharmac. Rev.* **14**: 175–223.

LONG, R. G. (1959). Modification of sensory mechanisms by subcortical structures. *J. Neurophysiol.* **22**: 412–427.

MORUZZI, G. and MAGOUN, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroenceph. clin. Neurophysiol.* **1**: 455–473.

POSTERNAK, J. M., FLEMING, T. C. and EVARTS, E. V. (1959). Effect of interruption of the visual pathway on the response to geniculate stimulation. *Science, N.Y.* **129**: 39–40.

SCHEIBEL, M. E. and SCHEIBEL, A. B. (1958). Structural substrates for integrative patterns in the brain stem reticular core. In: *Reticular Formation of the Brain* (JASPER, H. H. *et al.*, Ed.) pp. 31–55. Little, Brown, & Co., Boston.

SNIDER, R. S. and NIEMER, W. T. (1961). *A Stereotaxic Atlas of the Cat Brain.* University of Chicago Press, Chicago.

STERIADE, M. and DEMETRESCU, M. (1962). Reticular facilitation of responses to acoustic stimuli. *Electroenceph. clin. Neurophysiol.* **14**: 21–36.

SUZUKI, H. (1967). Effect of reversible retinal blockage on population response of the lateral geniculate nucleus. *Jap. J. Physiol.* **17**: 335–347.

SUZUKI, H. and ICHIJO, M. (1967). Tonic inhibition in cat lateral geniculate nucleus maintained by retinal spontaneous discharge. *Jap. J. Physiol.* **17**: 599–612.

SYMMES, D. and ANDERSON, K. V. (1967). Reticular modulation of higher auditory centers in monkey. *Expl Neurol.* **18**: 161–176.

TAKAORI, S., NAKAI, Y., SASA, M. and SHIMAMOTO, K. (1966). Central depressants and evoked click responses with special reference to the reticular formation in the cat. *Jap. J. Pharmac.* **16**: 264–275.