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# OBSERVATIONS ON EVOKED DENDRITIC POTENTIALS OF HUMAN CORTEX [1]

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## INTRODUCTION

Recently considerable evidence has been obtained indicating that the spontaneous electrical activity recorded from the surface of the brain is largely if not exclusively dendritic in origin. These data have been derived from electrophysiological and pharmacological studies (Clare and Bishop 1955; Tasaki *et al.* 1954; Purpura and Grundfest 1956b). It has been concluded that the 15-20 msec. surface negative wave evoked by direct or antidromic activation of cortical neurons is a synaptic potential of apical dendrites (Purpura and Grundfest 1956b). In addition, it has been shown that blockade of dendritic synapses by d-tubocurarine in the unanesthetized (Purpura and Grundfest 1956b) or nembutalized cat (Ostow and Garcia 1949) is associated with a transient abolition of the EEG. These data, while supporting the hypothesis formulated by Eccles (1951) and Li and Jasper (1953), that the spontaneous rhythms of the cerebral cortex represent synaptic potentials, also suggest that these synaptic potentials are generated in components of the post-synaptic dendritic membrane that is electrically inexcitable (Purpura and Grundfest 1956b). Further information relating to the important role of dendritic activity in the integration of complex neuronal patterns was obtained in studies with the psychotomimetic agent LSD (Purpura 1956 a, b). In the unanesthetized-succinylcholine paralyzed cat the mechanism of dendritic synaptic inhibition was reasonably accounted for on the basis of LSD activation of inhibitory post-synaptic receptors on apical dendrites (Purpura 1957). Because of the significance attached to dendritic activity, it was considered necessary to examine the properties of human apical dendrites with two major objectives in mind:

(1) To determine what differences if any might exist in the physiological organization of the pre- and post-synaptic components generating the dendritic potential; and

(2) To obtain information on the special pharmacology of human cortical synapses in order to relate the actions of various psychotomimetic and psychotherapeutic agents to known physiological events.

With these aims in mind, studies were initiated in four patients.

## METHODS

Routine operative exposures were carried out on 4 patients. Two patients subsequently underwent psychosurgery (bimedial frontal lobotomy) and 2 removal of neoplasm (astrocytoma, glioblastoma multiforme). In the latter cases studies were carried out on grossly normal appearing cortex distant from the suspected neoplastic regions. Following the craniotomies experimental procedures were immediately instituted. These usually began 3 to 4 hours after the pre-anesthetic medication which consisted of Demerol and scopolamine. Anesthesia was maintained with controlled nitrous-oxide oxygen mixtures supplemented with succinylcholine chloride-saline infusions for muscular relaxation.

Stimulation of the cortical surface was accomplished by a pair of fine teflon® coated silver wires (0.1 mm. diameter) held in a micromanipulator which was clamped to the

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bone margin. Stimulating and recording electrodes could be linearly adjusted for conduction velocity studies (fig. 2). Monopolar recording was used throughout the investigation, the stigmatic lead consisting of a small chlorided-silver ball-tipped electrode. The reference (indifferent) electrode was clamped to the cut bone edge. Other details of the stimulating and recording equipment have been described elsewhere (Purpura 1956a; Purpura and Grundfest 1956b; Purpura 1957). Multiple sweep registration of responses was generally employed unless otherwise stated to provide an indication of the degree of variability encountered.

In 3 of the 4 cases successful penetration of a small cortical artery supplying the area of cortex under investigation was accomplished by means of a special No. 31 gauge needle. A polyethelene catheter connected the needle to a three-way stockcock which permitted either normal saline or drugs to be locally injected. The later consisted of either d-tubocurarine chloride (3 mg/cc.) or d-lysergic acid diethylamide — 25 (LSD).[1]

## RESULTS

### A. *Effect of Nitrous Oxide.*

While it is clearly recognized that the pre-anesthetic medication employed routinely to insure a safe anesthetic course might contribute significantly in altering the normal responsiveness of dendritic synapses, it is of interest to note that no detectable difference in dendritic responsiveness could be attributed to the nitrous-oxide anesthesia employed. This was tested by recording dendritic potentials evoked by a surface stimulus 2.0 mm. from the recording electrode. As shown in figure 1, a conditioning and testing stimulus was utilized, the latter following the conditioning stimulus by 60 msec. In figure 1A considerable variation in the general background of activity can be observed while the patient was breathing a gas mixture of 80 per cent $N_2O$ - 20 per cent $O_2$. The superimposed records in figure 1B were made after the patient had been breathing 100 per cent oxygen for 10 min. While it appears that less background variability was detectable during the oxygen run, little or no effect was observed on dendritic responsiveness. Parallel studies carried out on laboratory animals have revealed essentially similar results (unpublished data).

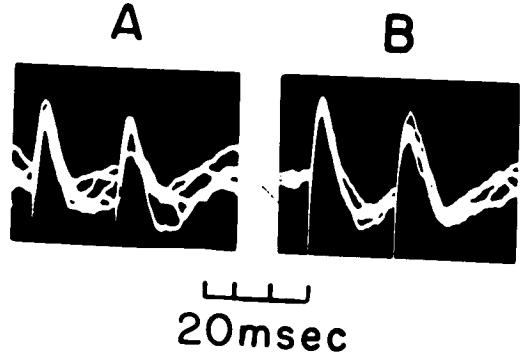



Fig. 1

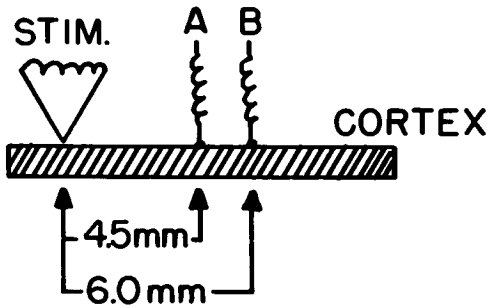
Dendritic potentials evoked by stimulation of cortical surface. Five consecutive superimposed tracings. In this and all subsequent records negativity at the recording electrode is signified by an upward deflection. Explanation in text. A: 80 per cent $N_2O$. B: 100 per cent $O_2$.

### B. *Pre- and Post-Synaptic Component of Dendritic Activity.*

Stimulation of the cortical surface evokes surface negative responses which can be detected as far away as 5 mm. (Adrian 1936; Chang 1951) to 10 mm. from the site of stimulation (Burns 1950, 1951; Rosenblueth and Cannon 1942). These observations have been interpreted as indicating that surface stimulation excites pre-synaptic elements in the molecular layer of the cortex which transfer excitation to apical dendrites along the extent of the horizontal elements (Eccles 1951; Purpura and Grundfest 1956). Similar studies carried out on the human cortex are exemplified in figure 2. The diagram illustrates the electrode arrangement which consisted of 2 monopolar recording electrodes placed at 4.5 mm. and 6.0 mm. from the stimulating wires. The difference in time between the onset of the activity at B and A is slightly under 3 msec. as shown by the 1000 c sec. calibration. This indicates a conduction velocity of 0.5 m/sec. assignable to the horizon-

[1] Generously supplied by Sandoz Co.

tal pre-synaptic fibers in the human cortex. What is of considerable interest, however, is the observation that 10 msec. were required for activity to arrive at electrode A, 4.5 mm. distant from the stimulating electrodes. It is inferred therefore that the additional 1.0 msec. is accounted for by synaptic delay which agrees with that calculated from Chang's (1951) data in the monkey.



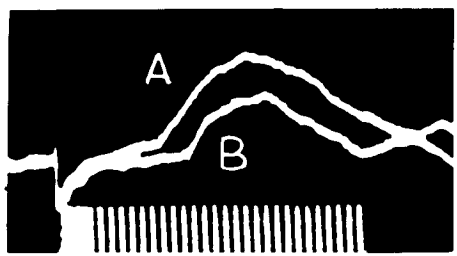




Fig. 2

Diagram illustrates recording and stimulating positions. Response A recorded 4.5 mm. from stimulating site and B recorded 6.0 mm. from same site. Further details in text. Calibration 1000 c/sec.

C. *Activity Cycles of Dendrites.*

Examples of the variability encountered in studies from patient to patient are shown in figures 3-5. In three cases examined in detail differences were noted in the responsiveness to conditioning-testing stimuli. Whereas summation of responses was clearly evident at stimulus intervals less than 10-12 msec., in no instance was the second response of greater magnitude than the same response unconditioned as reported in the cat (Clare and Bishop 1955). Another distinguishing feature was the variability in the depressed period of activity which commenced during the latter phase of the dendritic response. In the psychotic patients depression of the test

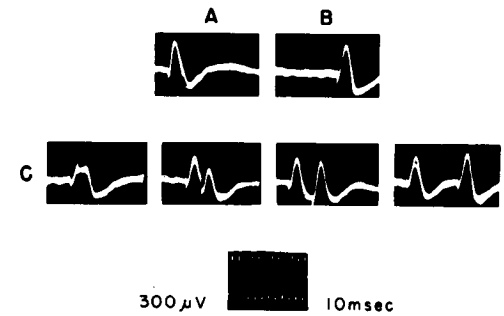



Fig. 3

Activity cycle of apical dendrites recorded from frontal cortex of first psychotic patient prior to psychosurgery. A, conditioning responses; B, testing responses; C, alterations of second response at varying times after conditioning shock. Note in C inhibition of second response 30-40 msec. after conditioning shock, and complete recovery at 45-50 msec. Five superimposed tracings throughout. Distance between stimulating and recording electrodes 2 mm.

response was apparent up to 40 msec. after the first stimulus in one case (fig. 3), but persisted for 100 msec. in the other (fig. 4). Little or no depressed phases were detectable in the tumor patients after the end of the

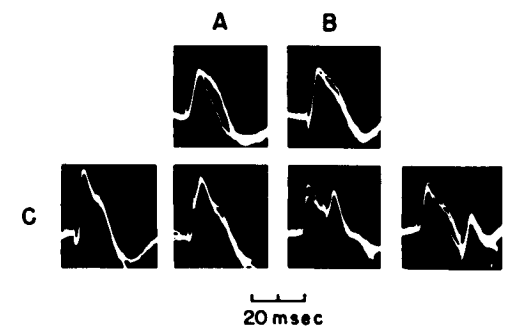



Fig. 4

Activity cycles recorded from frontal cortex of second psychotic patient prior to surgery. A, conditioning; B, testing responses. In C, note marked inhibition of testing response. Three superimposed tracings throughout. Distance between stimulating and recording electrodes 2 mm.

conditioning response. Some of the factors involved in these variations will be discussed below.

D. *Response to Locally Injected D-Tubocurarine and LSD.*

It has been demonstrated that in the cat intravenous administration of 3 mg/kg. d-tubocurarine reversibly abolishes the dendritic response evoked by direct stimulation of the cerebral or cerebellar surface or antidromic excitation of cortical neurons (Purpura and Grundfest 1956b). Considerably less sensitivity to d-tubocurarine blockade was noted for human cortical synapses. In figure 6, the effect of 3 mg. (total) of d-tubocurarine injected intra-arterially is shown. In this instance the cortical artery injected supplied the major part of the area investigated. Whereas the rapid injection of normal saline as a control (fig. 6B) caused some reduction in excitability which was associated with obvious blanching of the cortical area, slow infusion of d-tubocurarine produced a 30 per cent reduction in responsiveness (fig. 6C) with recovery beginning 5 min. later (fig. 6D). Although the sensitivity of dendritic synapses for d-tubocurarine blockade was found to be considerably less in man than in the cat, this was not true with regard to the action of the psychotogenic agent LSD. Slow infusion of LSD into a cortical artery resulted in a depression of evoked dendritic synaptic activity similar to that described in the cat (Purpura 1957). As in the d-tubocurarine injections control studies were also run utilizing rapid injections of normal saline in order to deliberately blanch the cortical area under observation. The sequence of events illustrated in figure 7 consists of the pre-injection conditioning and testing response in isolation (fig. 7A, B) and the depression of the second response when it falls 40 msec. after the first stimulus (fig. 7C). It should be pointed out that introduction of the No. 31 gauge needle into the cortical artery preceded the recording of the control responses (fig. 7A-C). During the registration of these potentials enough normal saline was injected into the cortical vessel to insure patency of the needle. Sudden pressure on the syringe resulted in blanching of the cortical area with concomitant reduction in both responses (fig. 7D) and recovery a few seconds later (fig. 7E). It is of interest to compare the effect of acute hypoxemia produced in this manner with the effect of 50 μg. LSD injected slowly in order *not* to blanch the cortex. Whereas both responses were depressed (fig. 7F), the first response

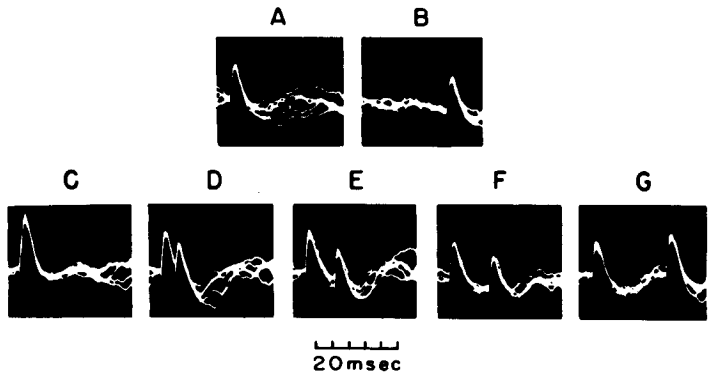



Fig. 5

Activity cycle of apical dendrites recorded from grossly normal cortex of patient with subcortical neoplasm. A, conditioning and B, testing responses. C, both stimuli applied together; D — G, varying intervals. Inhibition not detectable 20 msec. after first shock (D). Five superimposed tracings throughout. Distance between stimulating and recording electrodes 2 mm.

became less sharply peaked and during the testing response a delay was detectable prior to the rising phase, which persisted for minutes after the injection (fig. 7G). It is not clear why the positive component of the second response prominent in 7C was obliterated after LSD (fig. 7G).

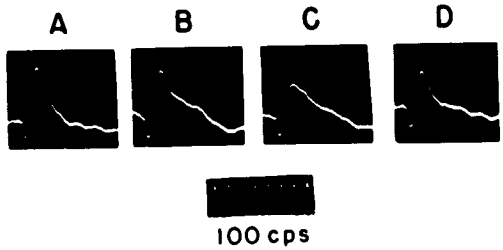



Fig. 6

Effect of local injection of 3 mg. d-tubocurarine on dendritic synapses into cortical artery after trial run with saline. A, control prior to rapid saline injection; B, during height of saline infusion; C, 30 sec. after 3 mg. d-tubocurarine and D, recovery 5 min. later.

## DISCUSSION

Physiological mechanisms such as are involved in excitation and conduction of activity along horizontal fibers in the molecular layer, generation and form of the dendritic synaptic potential, and estimation of synaptic delays, etc., are predictable on the basis of experimental observations on laboratory preparations. This is not true with respect to studies involving the organization of complex synaptic systems at the physiological and pharmacological levels. In these instances considerable caution must be exercised in translating results across species boundaries. Animal experimentation designed to explore cortical synaptic organization can only provide working hypotheses requiring suitable verification in human physiological studies similar to those described above. Abundant evidence is already at hand indicating a wide range of responsiveness of different synapses in the same and different species to identical pharmacological agents (Grundfest 1957). It is inferred from this that both qualitative and quantitative differences in biophysical processes may be operating to account for these results which have been generalized under the heading of "species specific differences".

Consideration of the foregoing factors may reasonably account for some of the differences in results that have been obtained in this preliminary investigation and which are at variance with results derived from animal experiments. Thus the relative insensitivity of human dendritic synapses to d-tubocurarine blockade immediately invites attention to these quantitative differences in synaptic pharmacology. It should be pointed

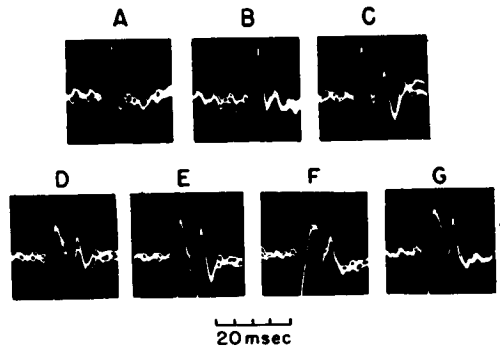



Fig. 7

Effect of local injection of LSD on dendritic synapses. A, conditioning; B, testing responses; C, together. Note augmentation of surface positive component of second response. D, reduction of both responses during rapid saline infusion and immediate recovery; E, F, 30 sec. after 50 μg. LSD and G, 5 min. later. The development of a detectable delay and abolition of the positive component (F, G) as well as a reduction of the negative components (F) is apparent. Three superimposed tracings throughout this series.

out that although d-tubocurarine is surprisingly impotent as a synaptic blocking agent in the human cortex, relatively less d-tubocurarine injected into the unanesthetized cat was previously found to reversibly abolish all central synaptic activity (Purpura and Grundfest 1956b). Interestingly enough, however, quantitative differences in sensitivity to d-tubocurarine blockade was also exhibited by different central synapses (Bernhard *et al.* 1951; Purpura and Grundfest 1956 a, b). Similar results have been obtained in cats with LSD which have been confirmed, in part, for the human cortex. The inhibition of human dendritic synapses by locally perfused LSD suggests that the in-

hibitory process operates in a fundamentally similar manner in cat and man. In the former the inhibitory effect has been ascribed to an activation of inhibitory post-synaptic receptors on dendrites (Purpura 1957) which are also available to inhibitory afferents either directly or through cortical inhibitory interneurons from the ascending brain stem reticular system (Purpura 1956 c, d).

The physiological counterpart of these pharmacological differences is exemplified by variations which have been found in the activity cycles of human apical dendrites to conditioning-testing shocks. While only depressed activity, which persisted for about 100 msec., was reported after a conditioning response in the lightly anesthetized cat (Clare and Bishop 1955), the fact that considerable variations in excitability have been detected in human cortex suggests that both excitatory and inhibitory synapses on dendrites are activated by the conditioning shock and that the interaction of opposing depolarizing and hyperpolarizing types of electrogenesis will determine overall responsiveness. That this indeed appears to be the case has already been demonstrated in animal experiments (Grundfest and Purpura 1956; Purpura and Grundfest 1956 a, b; Purpura *et al.* 1956). Whether or not any significance can be attached to the observation that inhibitory synaptic activity was prominent in the cortex of psychotic patients but not in the tumor patients, as evidenced by the differences in activity cycles, remains to be determined by future investigations.

## SUMMARY

1. Stimulation of the exposed human cortex evokes a 15-20 msec. surface negative response which is identical to the synaptic potential of apical dendrites as recorded in the cat.

2. The conduction velocity of horizontal fibers in the molecular layer is 0.5 m/sec. A central synaptic delay of 1 msec. is determined from conduction velocity studies with paired recording leads.

3. Whereas human dendritic synapses are relatively resistant to locally injected d-tubocurarine, LSD inhibits dendritic activity in a manner similar to that observed in the cat.

4. Variations in activity cycles of apical dendrites are believed to be accounted for by the interaction of opposing excitatory and inhibitory synaptic processes which determine overall dendritic responsiveness.

5. Discussion has focused on the significance of the suggestive differences in the pharmacological and physiological organization of cortical synapses in man and cat as they relate to hypotheses of drug actions determined solely in the latter species.

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