SYNAPTIC COMPONENTS OF CEREBELLAR ELECTRO-CORTICAL ACTIVITY EVOKED BY VARIOUS AFFERENT PATHWAYS*

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ABSTRACT

Electrical responses evoked in different regions of the cerebellar cortex of cat by stimulating various cerebello-petal pathways have been analyzed for their component postsynaptic potentials (p.s.p.'s). The principal analytical tools of the present work were pharmacological agents; the selective inactivator of depolarizing (excitatory) axodendritic synapses, γ-aminobutyric acid (GABA, or C_4); the homologous C_6 and C_8 ω-amino acids, which inactivate selectively the hyperpolarizing (inhibitory) axodendritic synapses; and the general inactivator of inhibitory synapses, strychnine. Some experiments employed the analytical possibilities of activity cycles.

The potentials evoked in one cerebellar region by different exciting pathways may differ markedly in their responses to drugs or may show different types of activity cycle. Also, the potentials evoked in various cortical regions by one cerebello-petal pathway are acted upon differently by the testing drugs. These differences are believed to be due to involvement of different proportions of excitatory and inhibitory, axosomatic and axodendritic p.s.p.'s. The analyses of a number of different responses confirm an earlier conclusion, that the cerebellar cortex is relatively lacking in inhibitory axodendritic p.s.p.'s in comparison with the cerebral cortex. Only the cortex of the paramedian lobule appears to be endowed with a considerable proportion of inhibitory p.s.p.'s, a finding which correlates with other data.

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INTRODUCTION

The electrophysiological and pharmacological differences which characterize some cerebral and cerebellar electrocortical activities were analyzed experimentally in previous papers (33, 34). These differences were accounted for on the basis of different synaptic organizations involved in the activities under study; "spontaneous" electrocortical discharges, as modified by bulbar-reticular stimulation, or responses evoked by direct stimulation of the respective cortical surfaces. It was concluded that relative to the responses of the cerebral cortex the cerebellar electrocortical activity evoked by stimuli directly to the cerebellar surface was markedly deficient in a surface-positive component. The latter, it is believed, represents hyperpolarizing, inhibitory postsynaptic potentials (p.s.p.'s) in the superficial cortical dendrites.

The different synaptic organizations postulated in this explanation may be expected to give rise to quite different reactions if the cortical activities in the two structures are challenged by drugs that act selectively to block either depolarizing or hyperpolarizing synapses (13, 24). This predicted difference was observed experimentally in the action of *d*-tubocurarine injected into heavily heparinized preparations (34), and of topical and systemic strychnine. It was also pointed out that the two cortical organizations might serve as test objects to differentiate central synaptic actions of drugs. On the basis of such tests it was shown that strychnine and metrazol have fundamentally different actions.

The remarkably distinctive effects that are produced by certain amino acids and related substances on the cerebral and cerebellar cortical responses evoked by directly applied stimuli (26–32) also appear to confirm the analysis. Depending upon their molecular structure (Fig. 1), some of these compounds invert the cerebral cortical response to direct cortical stimulation, but the same substances eliminate the corresponding cerebellar activity. The latter finding indicates that the drugs in question block the depolarizing p.s.p.'s of the superficial dendritic responses. The action of these is selective in that hyperpolarizing synapses are not affected. In the cerebral cortex this selective blockade should lead to unmasking of hyperpolarizing, surface-positive p.s.p.'s and this accounts for the inversion of the evoked electrical response by the drugs. In the cerebellar cortex, elimination of depolarizing p.s.p.'s can unmask only an insignificant amount of hyperpolarizing synaptic activity. This leads essentially to the elimination of the cerebellar cortical responses which are predominantly composed of depolarizing p.s.p.'s.

On the other hand, other drugs of this series augment markedly the cerebral dendritic response, but do not affect the cerebellar activity (Fig. 1). The explanation of these results is also consonant with the above. These synaptic agents appear to be selective blockaders of hyperpolarizing, inhibitory synapses, and like the similarly acting agent strychnine, they cause convulsive

electrocortical activity when topically applied to the cerebral cortex, but not when so applied to the cerebellar. Elimination of the inhibitory synapses in the cerebral cortical response would then account for the observed augmentation of the superficial, surface-negative dendritic p.s.p.'s. Since the corre-

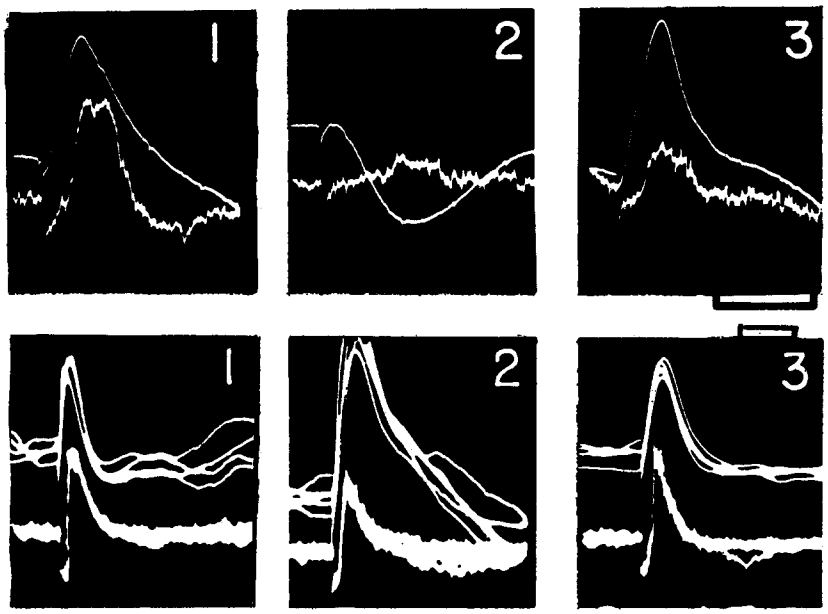

FIG. 1. Differential action of ω-amino acid drugs on cerebral and cerebellar electrocortical responses evoked by stimulating the respective cortex. Two experiments, upper row illustrating the effect of applying GABA, the lower, effects of C_6. The response evoked in the cerebral cortex (upper trace) and that produced in the cerebellar (lower trace) were recorded simultaneously. The surface-negative cerebral response became inverted upon applying GABA (column 2) while the cerebellar response was almost abolished. Column 3 shows the recovery of the potentials after rinsing away the GABA by flushing the cortical recording sites with Ringer's solution. In the experiment of the lower row, four consecutive traces are superimposed in each record to show the high degree of uniformity of the response. Application of C_6 to the recording sites augmented the cerebral response, but affected the cerebellar only slightly, diminishing it a little. Note the different time scales; calibrations 20 msec.

sponding cerebellar cortical response is deficient in the hyperpolarizing inhibitory synapses the application of the selective drugs would not, and does not, affect the cerebellar response.

The drugs of this series act with a high degree of specificity not only with respect to the electrogenic variety of the synapses, but also with respect to

synaptic varieties previously specified chiefly by anatomical data (6, 8); the axodendritic as opposed to axosomatic synapses (14–16, 22, 23, 26–30).

The availability of a series of drugs with so precisely specific and different actions permits their use to analyze synaptic organizations of different regions both of the cerebral and cerebellar cortex and of the same region activated by different neural pathways. This type of work has been in progress in this Laboratory during the past 2 years, and several aspects of the findings have been reported incidentally (14–16, 22–24, 30). The present paper deals with their employ in a systematic analysis of the various synaptic organizations in the cerebellar cortex that are activated by a variety of pathways. The work reported concerns only activity recorded from the cerebellar surface. Discussions of previous work dealing with cerebellar evoked potentials and of their interpretation will be found in the reviews by Bremer (2) and Dow and Moruzzi (9).

Methods

The general methods employed have been described in previous publications (30, 33, 34). Most of the experiments were done in neuraxially intact, succinylcholine-paralyzed cat preparations (33). In some experiments, however, decerebration was performed. These details will be noted at the time the relevant experiments are described. The electrical stimuli used were square pulses of brief duration, applied with the aid of three-coordinate manipulators through bipolar electrodes to cortical surfaces or to deep structures. In some experiments, various peripheral nerves were stimulated to evoke the response under study. As noted above, only superficially recorded evoked cortical activity was analyzed in these experiments. The responses were recorded differentially with monopolar active grid electrode and an indifferent reference electrode on the bone over the frontal sinus. They are shown in the records as negativity upward. For all the illustrations five consecutively recorded responses were superimposed. About thirty cats were used. Several systems were usually examined in each experiment.

All the illustrations of drug actions in this paper are from experiments in which one or several drops of the drug; 1 per cent γ-aminobutyric acid (GABA, or C_4), ϵ-aminocaproic acid (C_6), ω-aminocaprylic acid (C_8), or of 0.1 or 0.5 per cent strychnine sulfate were applied topically to the cortical surface in the region of the recording electrode. However, others of the amino acid series of drugs (30) were used with essentially identical results.

RESULTS

A. Actions of Synaptic Drugs on Different Cerebellar Sites and on Differently Evoked Activities

This section presents a few examples of the data obtained under different experimental conditions, prior to a detailed analysis of some evoked cerebellar potentials in terms of their component synaptic activities as revealed by the pharmacological agents.

1. Effects of Different Drugs on Cerebellar Response Evoked by a Peripheral Nerve.—Stimulation of a sciatic nerve produces a response (Fig. 2) with a well known sequence of potentials in the anterior homolateral vermian cortex (*cf.* reference 9). The early surface positivity contributed by the afferent impulses (7, 17) is succeeded by a prominent late surface positivity after some intermediate potentials of relatively variable form. The later positivity (Fig. 2, record *1*) is followed by negativity. Within a few seconds after applying

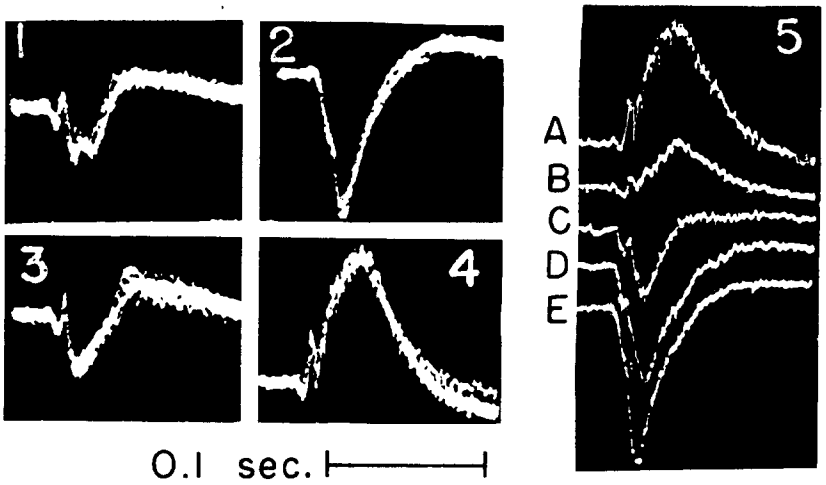

FIG. 2. Effects of synaptic drugs on cerebellar responses evoked by stimulating the sciatic nerve. Decerebrate cat, records from homolateral anterior vermis. *1*, control; *2*, after application of three drops of 1 per cent GABA to cerebellar cortical surface in region of recording electrode; *3*, 10 min. after rinsing cortex with warm Ringer's solution; *4*, after applying a few drops of 1 per cent C_6. *5*(*A*), response after applying C_6, (*B*), 2 sec. later. In the interval one drop of GABA (1 per cent) had been applied to cerebellar cortex. (*C–E*), responses at successive 2 sec. intervals after (*B*).

GABA to the vermian surface (record *2*) the evoked activity became a very large surface positivity lasting for about 50 msec. It was then succeeded by a large, longer lasting surface negativity. After flushing the cerebellar cortex with Ringer's solution for a few minutes, the response seen originally returned, but for some time there was still a trace of GABA after-action in the form of enhanced late negativity (record *3*). This has also been noted in other experiments (30). The application of ϵ-aminocaproic acid (C_6) to the same site produced an entirely different effect (record *4*). The evoked response now became predominantly surface-negative. The time courses of the inverted responses in records *2* and *4* differed to some degree. The positivity produced

after GABA started early and probably overrode the sharp negative component seen in the control responses (record *1*). The negativity which developed after C_6 (record *4*) retained the triphasic early sequence of the control, although both its negative peak and second positive trough were carried up on the newly developed negativity effected by application of the drug. The GABA-induced positivity was shorter than the negativity after C_6. Rather less striking, but nevertheless probably significant, was the persistence during application of C_6 of the background rapid cerebellar "spontaneous" activity which is diminished when GABA is applied. Also characteristic of cerebellar responses, as may be seen from subsequent figures, was the remarkable constancy of the responses to a given stimulus.

The rapidity of action of the drugs, as well as the interactive effects of the two is shown in the sequence of five individual traces of records *5*A–E. The uppermost response (A), resembling those seen in record *4*, was the activity evoked after treating the cerebellar cortex with C_6. A single drop of GABA was then applied in the 2-second interval separating records A and B. The prompt diminution and subsequent inversion of the response are shown as they developed in the course of the next few 2 second intervals. Less than 10 seconds after GABA had been applied, the response (E) was almost identical with that shown in record *2*.

2. Effects of the Different Drugs on Activity Evoked in Paramedian Lobule by Different Afferent Pathways.—The paramedian lobule apparently differs pharmacologically from the rest of the cerebellum in that strychnine topically applied to this cortex modifies its responses to some excitatory pathways. However, the drug does not affect the activity produced by other paths (*cf.* references 2, 18, and unpublished work in this laboratory). Fig. 3 shows three different types of experiments (A–C), all involving activity in the paramedian lobule, but in each case evoked by exciting a different pathway and reacting differently to the drugs. These responses have been described by a number of other workers (*cf.* reference 9). Stimulation of the inferior olive (A) resulted (record *1*) in an early sequence probably due to spikes in directly excited fibers (*cf.* reference 17), followed by surface positivity which was not particularly prominent relative to the spike activity. None of these potentials was affected by topically applied GABA (*2*) or by C_6 (*3*). This is an interesting correlation with the finding (18) that responses evoked in the paramedian lobule by stimulation of the inferior olive were not modified by strychnine when the latter was topically applied to the recording site.

The responses evoked by stimulating a region in the midpontine reticular formation (B) were quite different from those produced by stimulation of the olive (*cf.* also Figs. 12 and 13). They comprised (record *1*) a sequence of surface positivities including a very prominent late component. Topical application of GABA augmented and prolonged this last positivity (record *2*), but

application of C_6 (record *3*) did not affect the response. The same series of records also show the response evoked by a second equally strong stimulus delivered through the same electrodes approximately 40 msec. after the first. In the conditioned test only the early small positivity was seen (record *1*)

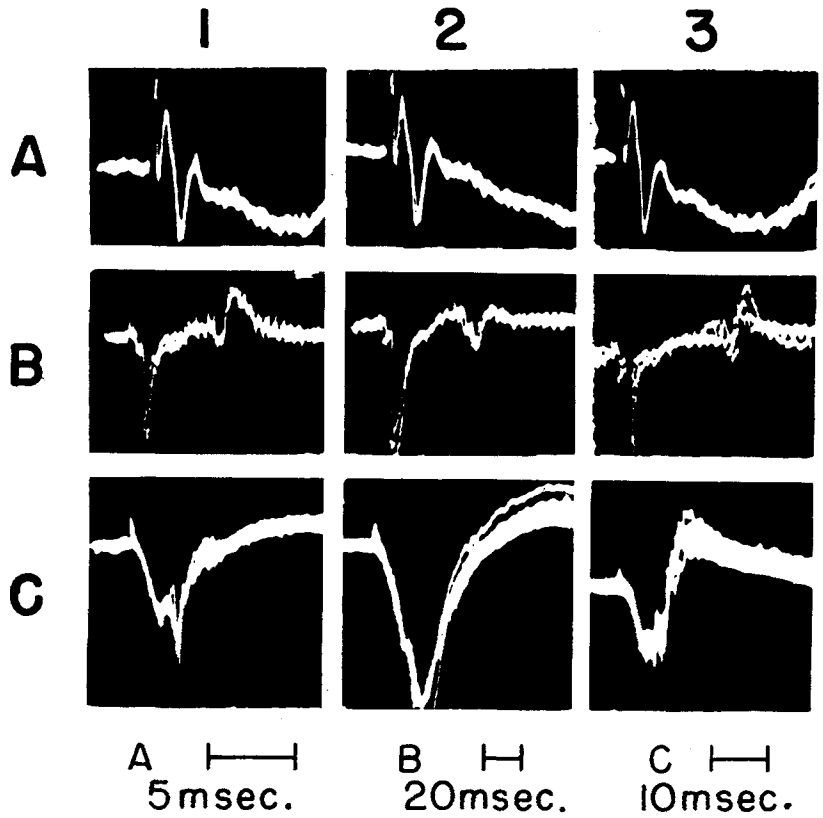

FIG. 3. Effects of GABA and C_6 on responses evoked in paramedian lobule by different pathways of stimulation. *A–C*, three different neuraxially intact succinylcholine-paralyzed preparations. Note different time scales of the recordings. In each experiment the records of column *1* show control responses; *2*, of responses after application of GABA (1 per cent); *3*, after applying C_6. *A*, stimulation of contralateral inferior olive. *B*, paired stimuli delivered to contralateral midpontine reticular formation. *C*, stimulation of contralateral posterior sigmoid gyrus.

and was followed by a potential not seen in the conditioning response, a small negativity lasting about 20 msec. Topical application of GABA (record *2*) inverted the negativity in the testing response into a briefer positivity which appeared as an elevation distinct from the initial positivity. A small negative

component terminated the response. The application of C_6 did not affect the conditioned response or the earlier, larger activity produced by the first stimulus.

Still another pattern of drug actions was produced in this cerebellar region when the responses were evoked by stimulating the contralateral posterior sigmoid gyrus (C) (*cf.* also Figs. 5 and 11). The cerebellar response in this case had two clearly distinct positive components (record *1*). Topical application of GABA augmented greatly the second positivity (record *2*), as was also

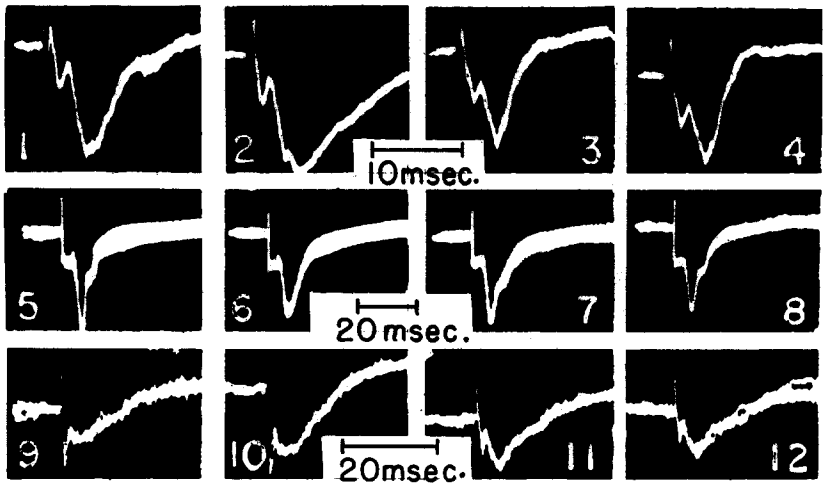

FIG. 4. Effects of amino acid drugs on cerebellar responses evoked by stimulating other cerebellar structures. Two decerebrate preparations. *1–4*, responses in posterior vermis to stimulation of fastigial nucleus. *1*, control; *2*, after GABA; *3*, recovery; *4*, after C_6. *5–12*, another preparation. *5–8*, recording in posterior vermis as above, but responses evoked by stimulating anterior vermis. Sequence of drug applications also as above. *9–12*, same preparation recording in right crus I on stimulating left crus I. Same sequence of drug applications as above.

seen in the vermian response to peripheral excitation (Fig. 2). The terminal, late negativity of the control response was also enhanced by GABA. However, unlike the case in B, topical application of C_6 altered the cerebellar response to the cerebral stimulation (record *3*). The second positive component was diminished and a negativity became prominent whose presence had already been suggested in the control response (record *1*).

3. Effects of the Synaptic Drugs on Different Intracerebellar Activities.—The next three examples (Fig. 4) show the effects of the amino acid drugs on potentials evoked in the posterior vermis (*1–8*) and in crus I (*9–12*). The experiments derived from two decerebrate preparations (*1–4* from one; *5–12* from another cat).

Stimulation of the fastigial nucleus evoked in the posterior vermis the potentials seen in record *1*. Topical application of GABA to the recording site augmented and prolonged the large positive component (*2*). The earlier polyphasic sequence of spikes was carried down on the large positivity. On the other hand, an application of C_6 (*4*) did not modify the potential.

The next sequence (*5–8*) shows that no significant effects were exerted by either GABA (*6*) or C_6 (*8*) on the response evoked in the posterior vermis on stimulating its anterior portion. Likewise, relatively little effect of the drugs was observed on the potentials evoked in crus I of the right cerebellar hemisphere by stimulating the homologous lobe of the left hemisphere (*9–12*).

B. Analysis of Cerebellar Synaptic Activities

The seven varieties of synaptically evoked cerebellar activities described in section A range from cases in which the potentials produced in some cerebellar regions by particular pathways were markedly and specifically affected by both varieties of synaptic drugs (Figs. 2, 3 C) through cases in which an effect was observed with only one of the drugs (Fig. 3 B, Fig. 4) or with neither (Fig. 3A, Fig. 4). This section presents other experiments of the same kind, but carried further, to analyze the probable synaptic organizations which underly the responses.

1. Analysis of Synaptic Activity in Paramedian Lobule Induced by Cerebro-cerebellar Pathway.—As already seen in Fig. 3 C, the paramedian lobule develops large potentials in response to stimulation of the cerebral cortex. The responses evoked by stimulating the pericruciate cortex are seen in Fig. 5. Each of the oscillographic records also shows first the activity evoked in the cerebellar cortex by a stimulus to its surface. This is surface-negative in the control records (*1* and *4*). The subsequent large positive response evoked by the cerebral cortical stimulation is clearly made up of two components, as was also the case in Fig. 3 C. Topical application of GABA (Fig. 5, record *2*) augmented the second positive component responding to the cerebro-cerebellar pathway (also seen in Fig. 3 C). However, the dendritic p.s.p. of the directly evoked response was eliminated. Only a brief, small diphasic sequence remained which was probably due to impulses in the directly excited fibers, but may also have included activity induced by these fibers at axosomatic synapses. On washing out the GABA the dendritic response returned as did the initial form and amplitude of the activity evoked by the cerebro-cerebellar pathway (Fig. 5, record *3*).

Record *4* shows another series of responses, prior to applying C_6. As was already noted above (Fig. 2), this drug did not affect markedly the directly evoked dendritic p.s.p. (record *5*). However, the effect of C_6 on the cerebro-cerebellar activity was also different from that produced by GABA (*2*). As was also seen in Fig. 3, the initial positivity was unaffected, but the second

positivity was now abolished and a surface-negative potential became prominent.

The central part of Fig. 5 shows enlarged records of responses from a control series (*4*), after GABA (*2*), and after C_6 (*5*) superimposed for comparison and analysis. The early positivity is seen to be an invariant component and

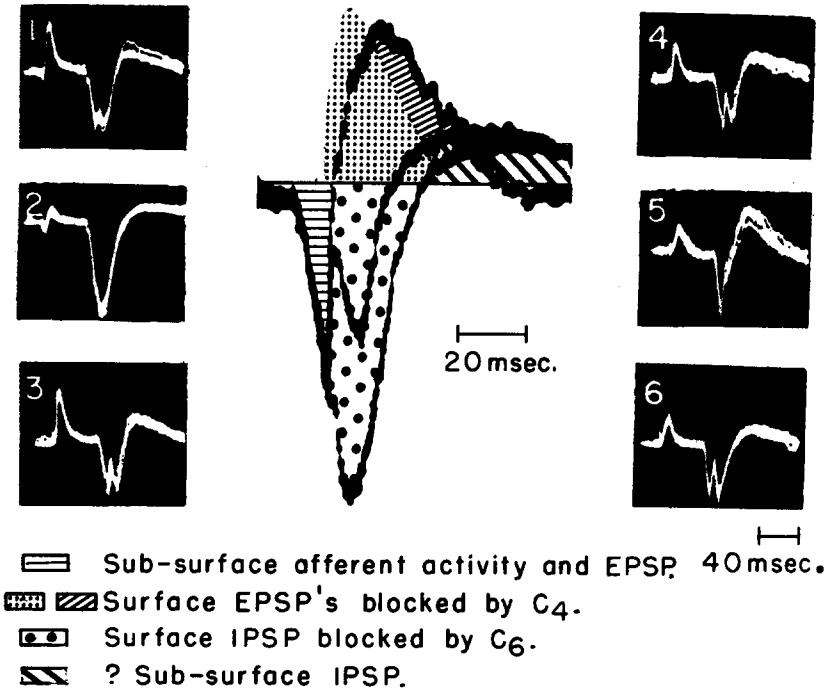

FIG. 5. Analysis of synaptic components in response of paramedian lobule evoked by stimulating contralateral pericruciate cerebral cortex. *1* and *4*, control responses. *2*, after applying GABA; *3*, reversal of drug action; *5*, after applying C_6; *6*, reversal of drug action. In each sequence a prior direct stimulus to the cerebral cortex also evoked a response. This surface negativity (*1*) was eliminated by GABA (*2*), but was not affected by C_6 (*5*). Thus, the directly evoked responses lacked an inhibitory component. *Center*, analytical construction showing the components involved in the cerebrocerebellar responses. Explanation in text.

this potential (area denoted by horizontal bands) can be ascribed to generators which are not affected by either synaptic drug. Certainly, the afferent volley components of the responses must be reckoned in this part, but their contribution to the activity may be expected to be small (15). Another component comprises the responses of axosomatic synapses (33) which are not attacked by the amino acid drugs (30). While both excitatory and inhibitory

synapses may be involved in that activity (11) the positivity recorded from the surface suggests that deep axosomatic e.p.s.p.'s predominate. The area of the late positivity which was disclosed in the response upon application of GABA (large dots) may be ascribed to a surface-positive potential of axodendritic hyperpolarizing (inhibitory) p.s.p.'s. In the control response this and the preceding portion were cut into and diminished by a surface-negative component ascribable to axodendritic depolarizing (excitatory) p.s.p.'s (de-

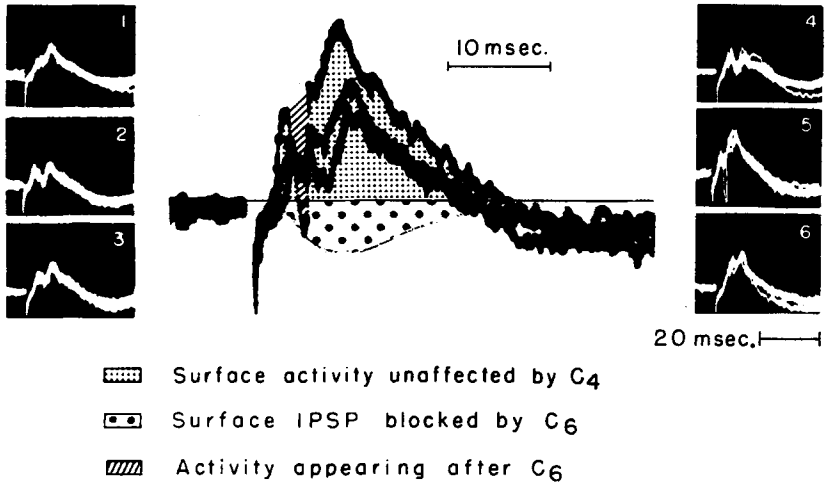

FIG. 6. Analysis of potentials composing the response in crus I to stimulation of the contralateral pericruciate cerebral cortex. *1*, control; *2*, after GABA; *3*, after rinsing the cerebellar cortex; *4*, control for the next sequence of records; *5*, after C_6; *6*, after rinsing cortex. The only component which is affected by the synaptic drugs is a small dendritic i.p.s.p. Its blockade by C_6 not only augments the surface-negative potential (*5*); the absence of the i.p.s.p. also brings out a new component, presumably a discharge of cells. Unanesthetized, succinylcholine-paralyzed, neuraxially intact preparation.

noted by small dots and thin diagonals). These two labile components of opposite sign that were affected specifically and differentially by the two drugs thus account for most of the potentials observed in records *2* and *5* and also provide a satisfactory reconstruction of the control response (*4*). A probable small later component (heavy diagonals) is less easily accounted for, but may be the surface negativity reflecting subsurface hyperpolarizing p.s.p.'s.

2. Cerebellar Synaptic Organizations Activated by Cerebro-Cerebellar Pathways. —Fig. 6 deals with the responses evoked in crus I on stimulating the contralateral pericruciate cerebral cortex. In the untreated cortex (*1*), or after wash-

ing it with saline solution (*3*, *4*, *6*), the response evoked by this pathway was a small, relatively brief two-component surface negativity. Application of GABA to the cerebellar cortex in crus I did not markedly alter the response (*2*). However, when C_6 was applied (*5*) two changes occurred. The surface negativity was enhanced, and early in its course there was frequently a brief, relatively large, positive-going spike.

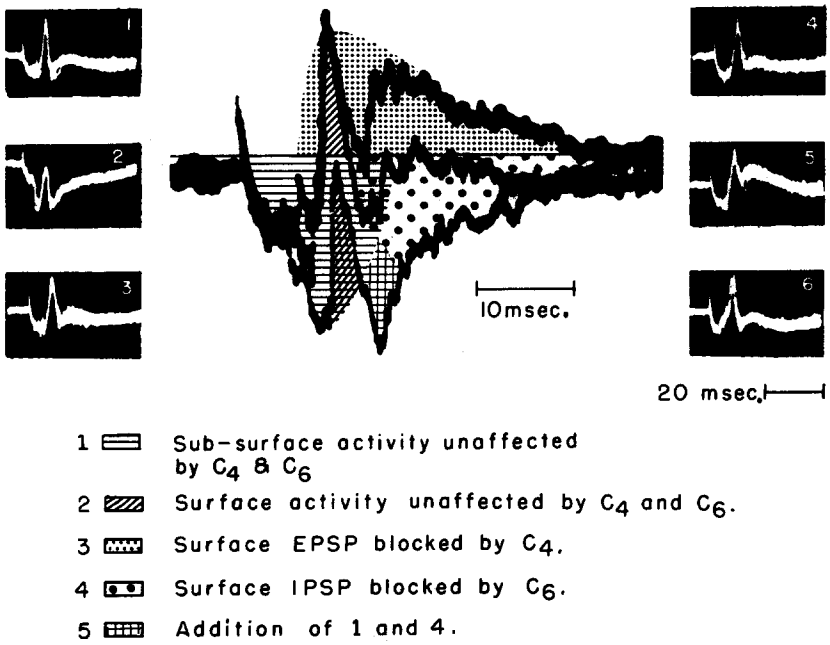

FIG. 7. The components of the response in crus II evoked by stimulating contralateral anterior sigmoid gyrus. Records taken in same sequence as in Fig. 6. *2*, represents effects of GABA; *5*, those of C_6. Neuraxially intact, succinylcholine-paralyzed preparation. Explanation of center figure in text.

The major element in the cerebellar response of this cerebro-cerebellar system appears to be a large surface negativity which is produced at synapses that are not affected by GABA or by C_6. Probably this is a response contributed by excitatory axosomatic synapses close to the surface of the cerebellar cortex. Although cell bodies do occur in these superficial layers (*cf.* reference 5), the origin of the potentials cannot be specified with the available data. A small component of surface-positive dendritic p.s.p.'s also appears to be present. When their response was blocked by C_6 the full negativity generated by the drug-resistant axosomatic synapses was then disclosed. However, the absence of inhibitory axodendritic p.s.p.'s then

also permitted further excitatory processes. This resulted in an early spike of the cell bodies which was manifested by the brief positive-going response.

More complicated activity was evoked in crus II (Fig. 7) by stimulating the contralateral anterior sigmoid gyrus. The potential was predominantly surface-positive. Out of the depth of this positivity arose a brief spike prominence, which probably was triphasic, but predominantly surface-negative. Topical application of GABA (record *2*) deepened the positivity, but did not affect the spike which was carried downward on the baseline of surface positivity. The application of C_6 (record *5*) also did not affect the spike. Out of its falling phase, however, there rose a new negativity.

Despite the apparent complexity of these records, their analysis in terms of p.s.p.'s is relatively simple. The largest portion of the surface-positive potential, including that part which was seen in the control responses (records *1* and *4*) or after reversal of the drug actions (records *3* and *6*) is produced chiefly by synapses that were not subject to blockade by either synaptic drug. The area in the center figure covered by horizontal lines denotes this potential. Also unaffected by either drug was the spike component (diagonal lines). Another surface-positive component which was normally masked and which was affected by C_6 (large dots) is a late dendritic i.p.s.p. All these potentials sum to produce the entirely positive-going response when GABA blocked the dendritic e.p.s.p. of considerable size. Only part of its surface-negative contribution was revealed by blockade of the late, small i.p.s.p. by C_6. The major portion was counterbalanced by the drug-resistant positivity. The spike arose during this early portion of the e.p.s.p. The level of the peak of the spike therefore did not change upon application of C_6.

3. The Synaptic Organization of Cerebellar Responses Evoked by Stimulation of Peripheral Nerves.—At one and the same site of the homolateral anterior vermis, near the midline, responses were evoked (Fig. 8) by stimulation of the radial nerve (*1–4*) and the sciatic (*5–8*). The initial responses to the two afferent volleys were essentially the same (*1*, *5*) and the effects of C_4 (*2*, *6*) and of C_6 (*3*, *7*) were also the same except for quantitative difference. In the center of the figure are superposed records of the initial small response, of the larger positive response after applying GABA, and of the still larger surface negativity produced by applying C_6. Obviously, the very large surface negativity disclosed by the latter drug cannot sum algebraically with the positivity after GABA to produce the net positive potential of the control response.

Several explanations can probably be devised to account for this discrepancy. An appealing one, which takes into consideration the physiological fact that blockade of inhibition leads to "excitatory" phenomena, is the assumption that an additional synaptic pathway is opened when inhibitory activity is blocked by C_6. The predominantly surface-positive response of the untreated cortex is apparently due chiefly to activity of synapses that are not

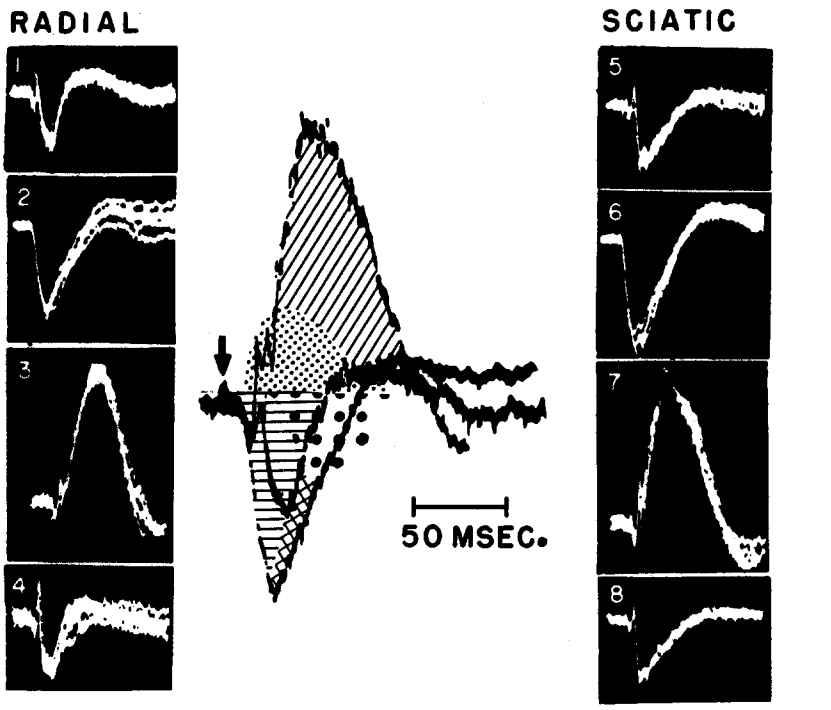

FIG. 8. Analysis of postsynaptic potentials contributing to the cerebellar responses evoked by stimulation of radial and sciatic nerves. Decerebrate preparation, all records made from one recording site on the anterior vermis, near cerebellar midline. *1–4*, stimulation of homolateral radial nerve, and *5–8*, of homolateral sciatic nerve. Initial control responses *1* and *5*. Responses after applying GABA *2* and *6*; after applying C_6, *3* and *7*; after rinsing cerebellar cortex *4* and *8*. *Center figure*, superposed records of control response, of that after GABA, and after C_6 produced by stimulating the radial nerve. The surface-positive potentials have a large component (horizontal bars) which represents chiefly axosomatic p.s.p.'s and a smaller positivity (large dots) which is contributed by hyperpolarizing (inhibitory) dendritic p.s.p.'s. Both sum to make up the response seen on applying GABA. In the response of the untreated cortex only a small surface-negative excitatory dendritic p.s.p. is generated (small dots). When the inhibitory synapses are blocked by C_6 a second, normally inhibited synaptic system is brought into activity and this gives rise to a large surface negativity shown by the diagonal lines.

affected by either type of amino acid drug (horizontal lines). This activity is fully disclosed when GABA blocks the smaller surface-negative contribution of the axodendritic excitatory synapses (small dots). However, the positivity then also comprises a small component of axodendritic inhibitory p.s.p.'s (large dots). When the latter activity is blocked by C_6, the net excitatory

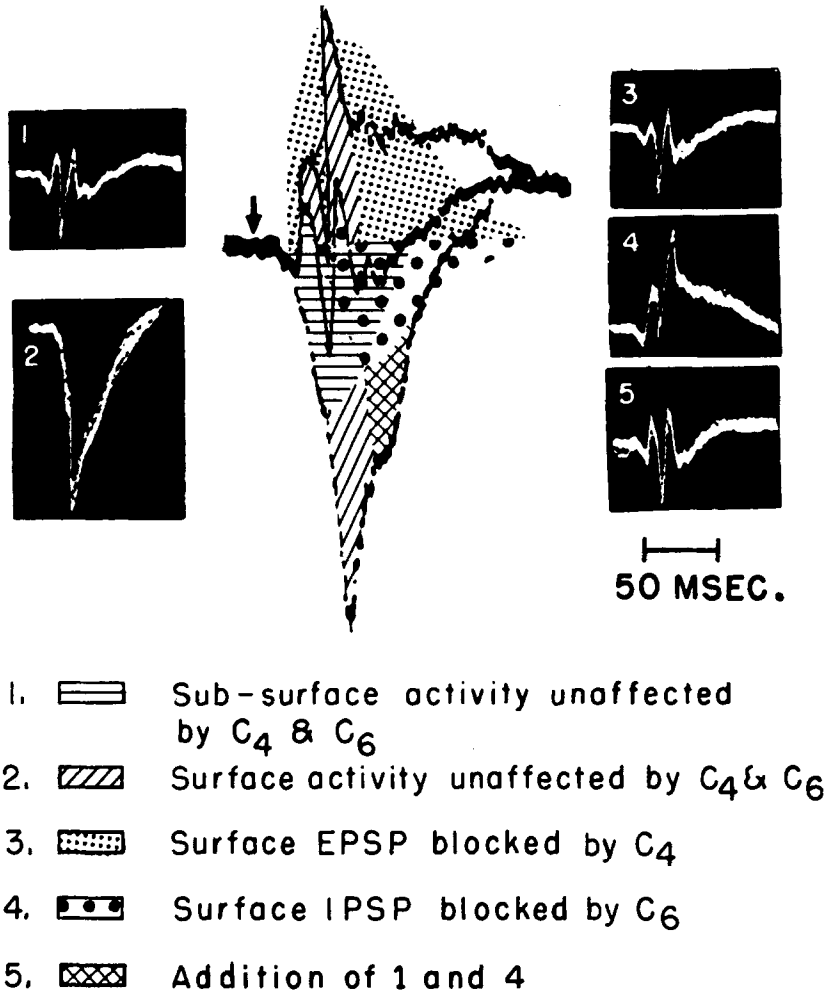

FIG. 9. Components of the response evoked in a more anterior region of the vermis by sciatic stimulation. Decerebrate cat. Records *1* and *3*, controls; *2*, after application of GABA to the cerebellar recording site; *4*, after application of C_6; *5*, reversal of the response to the initial type after rinsing the cerebellar cortex. Analysis of center figure in text.

effects bring on a new activity (diagonals) which is surface-negative and presumably is composed largely of axodendritic excitatory p.s.p.'s.

The explanation offered above is, in sum, that a pathway which normally is not active because of the occurrence of i.p.s.p.'s becomes activated by the afferent volley when the inhibition is blocked. This accords also with the data for another system previously presented in Fig. 6. The augmentation of surface negativity caused by C_6 (record *5*), and probably due to elimination of i.p.s.p.'s, produced a spike. The similarity of the effects produced by the drugs on the responses to sciatic stimulation and those to radial stimulation indicates that the same general phenomena are to be expected in both cases.

In a decerebrate preparation, recording about 6 mm. anterior to the site from which the records of Fig. 8 were made, the vermian midline response to sciatic stimulation was that shown in Fig. 9 (records *1*, *3*, and *5*). The response, recorded on a slow sweep to show its full time course, was predominantly positive, but this positivity was interrupted by several relatively rapid changes in slope which resulted in the manifestation of a spike-like sequence, including brief transitions to surface negativity. Topical application of GABA smoothed out the activity and the response became a large, long lasting surface positivity (*2*). On the other hand, topical application of C_6 inverted the dominant positive potential into surface negativity (*4*). The spike-like activity of the initial response (*1* and *3*) was still manifested, but was carried high on the negativity.

The complete sequence, nevertheless, can be resolved into the same basic components that were inferred for the previously analyzed responses. A large initial positivity (marked by horizontal lines of the center diagram in Fig. 9) and a positive-negative sequence (diagonal lines) are both considered to be insensitive to the synaptic drugs. A very large component of dendritic e.p.s.p.'s is present from the beginning (small dots) in contrast to its onset in the response of Fig. 8 only when the i.p.s.p.'s were blocked. As in the former response, the i.p.s.p. which was blocked by C_6 (large dots), is relatively small and develops late. Thus, the activity evoked in both vermian regions by the peripheral stimulation has essentially the same synaptic components except that in the posterior region (Fig. 8) part of the pathway which evokes the dendritic e.p.s.p. was subject to blockade by the i.p.s.p.

C. Comparison of Action of Strychnine and Amino Acid Drugs

Strychnine, as a selective blockader of inhibitory synapses (*cf.* references 10, 20, 33, 34), in large measure acts on the cerebellar cortex (Fig. 10) as do the larger chain ω-amino acids (Fig. 5). The surface-negative responses evoked in the paramedian lobule by stimulating this cortex were not affected by strychnine (Fig. 10 *a*, *b*). Furthermore, the response at the same site evoked by a stimulus to the contralateral pericruciate cerebral cortex was changed by

strychnine (Fig. 10 *c*, *d*) in exactly the same way as the identical response was changed by C_6 (Fig. 5). In both, the second positive peak of the response was eliminated and a large, long lasting negativity was introduced.

However, the action of the ω-amino acids is confined, apparently rather strictly, to the axodendritic synapses of the vertebrates (30). Since strychnine

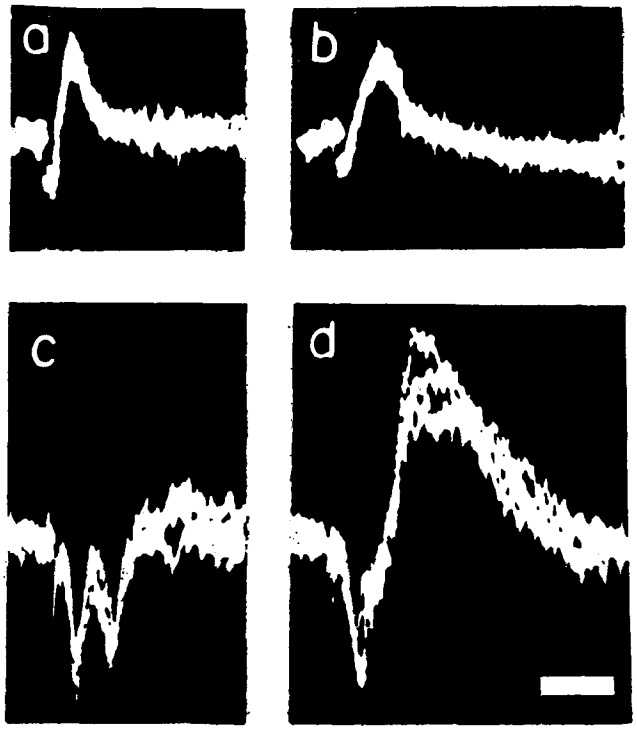

FIG. 10. Effects of topical strychnine on differently evoked responses in paramedian lobule. Response evoked by stimulus to cortical surface (*a*) was not affected by 0.5 per cent strychnine (*b*). The response at the same recording locus evoked by stimulating contralateral pericruciate cerebral cortex (*c*) was affected (*d*). Compare identical effects of C_6 on the same responses in another experiment (Fig. 5). Calibration 20 msec.

eliminates inhibitory p.s.p.'s recorded intracellularly in motoneurons (10, 20), it is highly probable that this drug blocks the axosomatic as well as the axodendritic inhibitory synapses. Therefore, if the electrocortical activity involves a large proportion of axosomatic synapses the actions of the amino acid drugs and of strychnine should differ. The divergence may be expected to be larger the more the response involves axosomatic synapses. The experiment of Fig. 11 involved responses in which, as was shown above (Figs.

8 and 9), axosomatic synaptic activity is strong. This type of response therefore showed the largest differences between the action of strychnine and the amino acids. Nevertheless, it also exhibited a considerable degree of similarity of action. The interaction between strychnine and GABA (Fig. 11 *g*)

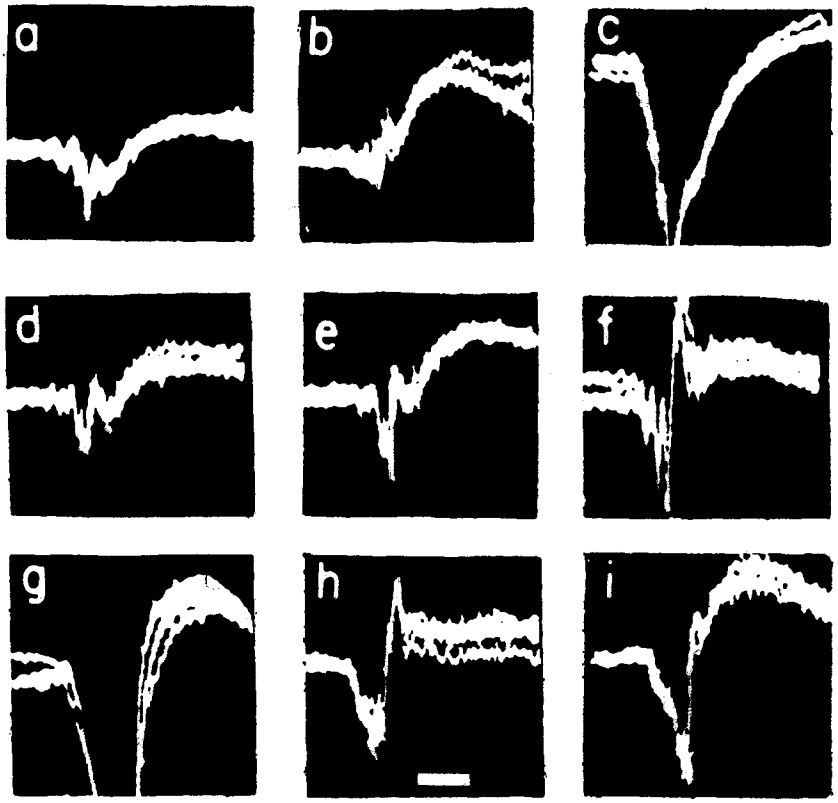

FIG. 11. Comparison of actions of strychnine and amino acid drugs on vermian response evoked by sciatic stimulation. *a*, initial response; *b*, effect of C_8; *c*, responses 10 to 20 sec. after applying a drop of GABA at recording site; *d*, after flushing cortex; *e*, 0.1 per cent strychnine; *f*, 0.5 per cent strychnine; *g*, 10 to 20 sec. after applying 2 drops of GABA; *h*, after flushing cortex; *i*, effect of C_6.

was similar to that between C_8 and GABA (*c*) or between C_6 and GABA (Fig. 2).

The response evoked in Fig. 11 was essentially the same as that of Figs. 2 and 9. The application of C_8 in the present experiment (Fig. 11 *b*) had a similar effect to that produced by C_6 in the former (*4* in Figs. 2 and 9). In both cases GABA (Fig. 11 *c*; Figs. 2 and 9, records *2*) changed the response into a strikingly large, long lasting positivity. The effect of weak strychnine (0.1

per cent; Fig. 11 *e*) was somewhat like that of C_8 (*b*), but the strychnine brought out an early spiking activity. The latter became much more pronounced on applying stronger strychnine (0.5 per cent, *f*) while the late negativity was somewhat diminished. Nevertheless, when GABA was applied an even larger positivity developed (*g*) than after C_8 (*c*). It may be noted that in both cases the action of GABA must have been in addition to that of the previously applied drug. The responses on flushing the cortex (*d*, *h*) still resembled the responses which were produced by C_8 or strychnine alone. This indicates that the initially applied drug was still present during the action of GABA. That the strychnine was still active is further borne out by the effect produced on subsequently applying C_6 (*i*). The large, late negativity which developed was preceded by an early large surface positivity to which spiking activity was clearly contributory, as in *f*.

The axodendritic components of the potentials in the response of Fig. 11 *a* are probably similar to those deduced in the responses of Figs. 8 and 9, a large surface-negative component and a small surface-positive one. In the present case, as in the earlier, the activity includes a large component of axosomatic p.s.p.'s which cause surface positivity and therefore probably represent a net of excitatory p.s.p.'s. How large these potentials are cannot be evaluated quantitatively with the available methods, but that they are large may be concluded from supplementary data. The application of GABA on a cortex already treated with C_8 (*c*) or strychnine (*g*) produced a deep positivity as did the application of GABA alone in the experiment of Fig. 9 (record *2*). Since the inhibitory axodendritic synapses were blocked by the C_8 and probably all inhibitory synapses were blocked by the strychnine, it may be concluded that the predominant electrocortical activity is that of axosomatic excitatory synapses which registers as surface positivity. Next largest, and almost large enough to counterbalance the positivity, is the surface-negative activity of the axodendritic excitatory synapses. The dendritic inhibitory p.s.p.'s appear to be small (*cf.* Figs. 8 and 9), and so probably are the axosomatic i.p.s.p.'s. Nevertheless their effects are discernible in several ways. As was already deduced in the case of the response of Fig. 8, blockade of the axodendritic i.p.s.p.'s can lead to later, large surface negativity (Fig. 11 *b*). Absence of the axosomatic i.p.s.p.'s, as well, induces excitatory activity (*f*) which probably involves axodendritic synapses as well as the axosomatic and cell discharges. This accounts for the appearance of spikes and a relative absence of slower potentials, which are of opposite polarities.

D. Electrophysiological Manifestations of Some Differences in Synaptic Organizations

An earlier paper (34) described several varieties of correlations by which the electrophysiological properties of the cerebellum reflected its specific synaptic organization. This section describes several others that are an out-

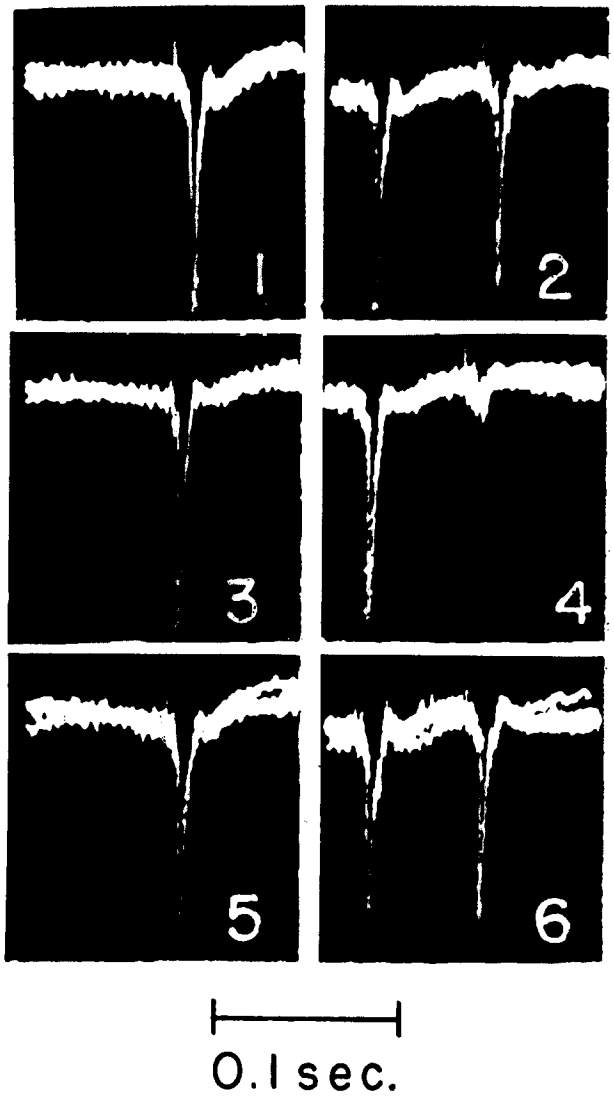

FIG. 12. Different electrophysiological effects produced in correlation with apparently identical cerebellar activities. Recording electrodes on surface of paramedian lobule. Stimuli delivered to upper pontine reticular formation. *1*, *2*, cerebellar responses to single and paired stimulations. The testing response in *2* was not greatly affected by the conditioning activity which preceded by about 60 msec.; *3*, *4*, responses at same recording point evoked after stimulating electrodes were raised about 1 mm. in the pons. The single response (*3*) and the conditioning activity (*4*) were not distinguishable by magnitude or time course from their homologs in *1* and *2*. The testing stimulus following the conditioning activity by 60 msec. in this case elicited only a small response. *5*, *6*, the stimulating electrodes were lowered again to the original site and produced the same effects as seen in *1* and *2*.

growth of the present, chiefly pharmacological, analysis of cerebellar synaptic systems.

The potentials evoked in the paramedian lobule by a stimulus to the upper pontine reticular formation were shown in Fig. 3 B and are seen again in Fig. 12. Overtly, the large surface-positive response appeared identical when it was elicited by stimulating various sites in the pons (Fig. 12, records *1*, *3*, and *5*). However, important differences were disclosed by applying paired stimulations (records *2*, *4*, and *6*). Stimulating at one site evoked the paired responses seen in record *2*. There was only a little diminution in the test response when the testing stimulus was preceded some 60 msec. earlier by a conditioning activity (*1*). For records *3* and *4* the stimulating electrodes were about 1 mm. deeper in the pons. The single response (*3*) was essentially identical in magnitude and time course to that elicited by the previous stimulation. The conditioned testing stimulus, however, no longer produced the large surface-positive response (*4*). Thus, the ponto-cerebellar pathways coursing at different depths in the pons involved divergent cerebellar synaptic organizations. The differences were not manifested overtly in the evoked potentials, but were disclosed by long lasting effects as development of marked inhibition leading to a change in the basic form of a second response in one case, but not in the other.

The experiments presented in Fig. 13 show that the effects illustrated in Fig. 12 are to be ascribed to inhibitory processes, rather than to "refractoriness." The cerebellar responses were evoked in the paramedian lobule by stimulating as in Fig. 12, but at a lower point in the contralateral pons. The individual responses (*1* and *7*) to maximal stimuli were large surface-positive potentials. When paired maximal stimuli were delivered at different intervals the effects were dependent on the interval. When the testing stimulus was delivered soon after the conditioning response (interval about 10 msec.; *2*) it developed a relatively large complexly shaped activity. However, the testing response decreased at longer intervals (*3*, *4*), the most prominent component being a surface negativity (also seen in *2*) which was absent or very small in the single response (*1* and *7*). At an interval of 75 msec. the testing stimulus evoked no response at all (*5*), but at still longer intervals the response returned to its initial form, although after about 120 msec. (*8*) it still had not recovered to full amplitude. These results indicate that a sequence of inhibitory and excitatory events follows the overt evoked potential. Not associated with overt electrocortical activity, these events can be detected by the activity cycle (25, 36, 37).

Another way of affecting the testing response which provides additional information is shown in the sequence of records *7* through *12* of Fig. 13. The maximal testing response (*7*) was preceded (*8–12*) by progressively increasing conditioning activity evoked about 40 msec. before the testing response. A

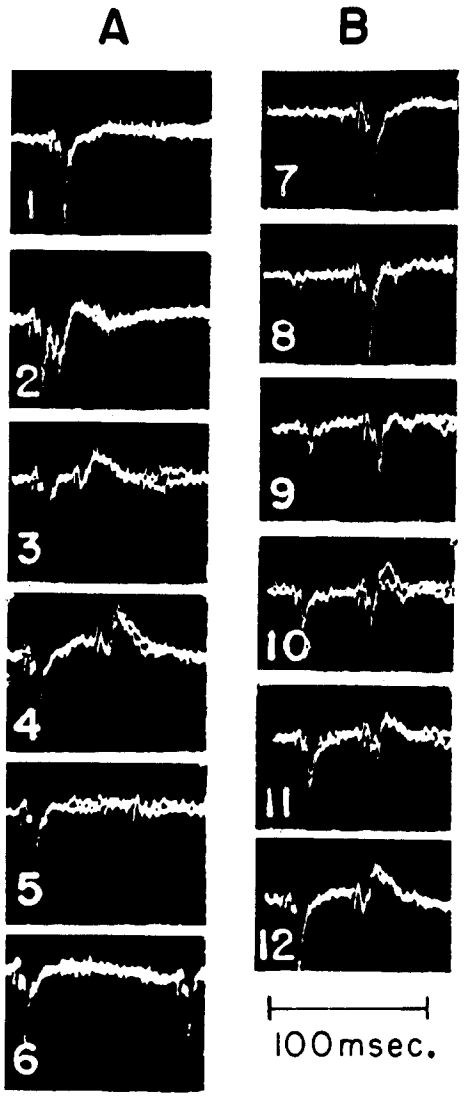

FIG. 13. Demonstration of inhibitory effects in cerebellar activity. All responses recorded from one site in paramedian lobule. Activity evoked by stimulating in contralateral midpontine reticular formation. *A*, activity cycle. A maximal testing stimulus which evoked responses seen in record *1* was applied at different intervals after a conditioning activity. Intervals are 10 msec. (*2*); 30 msec. (*3*); 45 msec. (*4*); 75 msec. (*5*); and 125 msec. (*6*). Note that the testing response was larger at the shortest interval (*2*) than at the longer (*3*–*5*). Also, that a negative component in the conditioned activity developed which was not present in the unconditioned testing responses. *B*, change in the maximal testing response on gradually increasing size of a conditioning response evoked approximately 40 msec. earlier. Testing response alone (*7*). This response was not affected by the smallest observed conditioning stimulus (*8*), but was markedly decreased (*9*–*11*) by very small conditioning activities. The maximal reduction in the size of the testing response was attained with weak conditioning stimuli (*10*–*12*) and this level was associated with development of late negativity.

small conditioning response (*10*) markedly affected the testing response, and its diminution therefore cannot have been caused by "refractoriness" of previously excited cerebellar units. The decrease in the testing response became maximal long before the conditioning activity attained maximum amplitude. Therefore, in no component along the pathway had all the units been excited by the weak conditioning volleys. The effect on the testing response thus must be ascribed to inhibition. It will be noted further that the testing response developed a surface negativity that was not present in the unconditioned response or in any of the conditioning activities of different amplitudes.

DISCUSSION

The cerebellar cortex has a relatively simple anatomical organization since its cellular composition is limited as well as highly ordered (5). Nevertheless, the many attempts (*cf.* references 2, 9) that have been made in the past two decades to analyze the electrophysiology of this apparently simple structure have only emphasized its functional complexities, both with respect to intracerebellar events and the afferent and efferent extracerebellar relations. These differences are illustrated by the fact that cerebellar potentials evoked by stimulating various peripheral or central pathways are almost all predominantly surface-positive. On the other hand, the responses to stimulating the cortical surface itself are predominantly and, perhaps, almost exclusively surface-negative.

The data presented in this paper analyze some of the complexity in terms of the different synaptic substrates that are brought into activity by different pathways to the same cerebellar site or by one pathway which evokes activity in different sites.

At this point it is useful to recapitulate methods that have been employed in previous attempts to analyze the potentials evoked in cortical surface. Random or spontaneous potentials are, in general, not well suited to such analysis in the case of the relatively undifferentiated activity of the cerebellar cortex. However, drug-induced "spontaneous" activity in the form of the "cerebellar strychnine tetanus" (21) has been employed analytically (34). The analytical employ of evoked cerebellar activity in the simplest case involves deductions from measurements of latencies and durations of responses, and from their sequence (7, 17). Various attempts at analysis of individual activities of cerebellar cells have been made (*cf.* references 1, 3, 11, 38). While this approach has considerable appeal, in practice it has to date contributed little new information regarding the specific nature of cerebellar activities.

As has been shown in the foregoing, and also in other papers from this laboratory (25, 33, 34, 37) and from others (*e.g.*, reference 4), cortical potentials that appear to have the same form and are equally prominent may have different origins and may bring in their train vastly different physiological

manifestations. For this reason still other tools need to be employed. Illustrated in this paper, but developed with greater detail elsewhere (23, 25, 34, 37) is the analysis of synaptic organization by combining the study of activity cycles and of the effects of repeated stimulations on the electrophysiological characteristics of the responses. The present paper concentrates chiefly on the use of selectively acting synaptic drugs as a combined analytical tool together with the electrophysiological criteria of form, timing, and sign of responses.

The analytical interpretation of the effects of drugs on electrocortical potentials involves two factors; the initial assumptions regarding the nature of the potentials, and the significance attached to the action of pharmacological agents. These are interlocking assumptions, for the conclusion that the electrocortical activity is chiefly the manifestation of p.s.p.'s (33, 34) leads to specific interpretation of the actions of drugs in terms of a general theory of neuropharmacological mechanisms (12, 13, 16). It is the success of both assumptions in accounting for a wide variety of phenomena in electrocortical physiology and pharmacology that must be considered as the pragmatic test of their relative validity.

The present experiments provide additional confirmation that the long chain amino acids act as blockaders of inhibitory synapses. A response which was not affected by strychnine (Fig. 10) also was not affected by C_6 (Fig. 5), whereas responses of other types evoked in the same cortical region by different afferent excitatory pathways were affected identically. Likewise, the differences which can be demonstrated between the actions of strychnine and of the ω-amino acids support the conclusion (30) that the latter drugs act selectively on the axodendritic synapses. The resistance of the surface-negative response (Figs. 5 and 10) to both strychnine and C_6 confirms the further conclusion that the longer chain amino acid drugs do not act on the axodendritic e.p.s.p.'s which are, however, blocked selectively by GABA (Figs. 1 and 5). Nevertheless, some lack of specificity cannot be ruled out, particularly since the related guanidino acid drugs show a considerable degree of cross-action.

Another source of error arises from the nature of the system being analyzed and the available methodology. The electrocortical potentials are believed to be the resultants of four p.s.p.'s. The axosomatic e.p.s.p.'s and axodendritic i.p.s.p.'s should both contribute to the surface positivity while the axosomatic i.p.s.p.'s and the axodendritic e.p.s.p.'s should be the sources of the surface-negative components. If drugs were available that could make these potentials pharmacologically distinguishable, these four unknown terms could, perhaps, be analyzed precisely. Lacking a full complement of specifically acting drugs the solutions can only be approximated.

Another factor interferes with the analysis. Blockade of synapses does more than eliminate the p.s.p.'s of these synapses. Elimination of inhibitory "brak-

ing" makes possible many varieties of activity that are not normally present, as is denoted by the convulsant action of strychnine and the longer chain amino acid drugs. In some of the figures of the paper it will be noted that the inactivation of inhibitory synapses tended to increase the high frequency background activity of the cerebellar cortex (*cf.* references 2, 9). GABA tended to decrease both the "spontaneous" and the drug-induced spike-like activity.

Finally, a limitation may be mentioned which derives from the fact that the recordings are all extracellular and therefore do not provide standards for an absolute comparison of potentials from one experiment to another. However, the rather close similarities in the potentials obtained in different experiments of a given type (*cf.* Fig. 2, 9, 11, and Figs 5 and 10) and the similarities of the responses to drugs in these cases affirm the validity of the present conclusions.

In the course of the present exploration of different synaptic organizations in the cerebellar cortex, very large divergencies were deduced in the synaptic compositions of the variously evoked responses. The extreme case is the response produced by direct cortical stimuli, which is considered to be almost entirely a dendritic depolarizing p.s.p. superimposed on the spikes of the initiating volley (Figs. 1, 5, and 10). In all but one of the varieties of activity that have thus far been analyzed the hyperpolarizing dendritic p.s.p.'s have been small, relative to the large component of this activity that appears to exist in the cerebral cortical response (33, 34). Only the response evoked in the paramedian lobule on stimulating the contralateral pericruciate cerebral cortex (Figs. 5 and 10) appears to have a large inhibitory dendritic p.s.p component. Jansen (18) also found that this surface was particularly affected by applying strychnine to the recording site. It may be noted, incidentally, that the response evoked in this region by surface stimuli is surface-negative and chiefly composed of axodendritic e.p.s.p.'s, as it also is in the vermian cortex (Fig. 1). The latter region, however, has a relatively smaller complement of inhibitory synapses (Figs. 2, 8, 9, and 11). In crus I (Fig. 6) the activity evoked by stimulating the pericruciate cerebral cortex apparently lacked a dendritic e.p.s.p. component. Nevertheless, the over-all response was negative because of drug-resistant surface-negative activities which far outweighed the small dendritic i.p.s.p. that was susceptible to blockade by C_6. The response evoked in crus I by stimulation of the contralateral crus I lacked even this small component (Fig. 4, records *9–12*), since the responses were not affected by either GABA or C_6. In all the other cerebellar systems tested the dendritic e.p.s.p.'s affected by GABA were larger than the i.p.s.p.'s which were blocked by C_6 or C_8.

Although the inhibitory component seen in Fig. 6 was small, its blockade nevertheless could lead to spikes which were probably due to augmented axosomatic synaptic excitation. Topical applications of C_6 to the cerebral cortex

(30) or injections after blood-brain barrier lesions do not modify spike activity discharged into the pyramidal tracts on strong stimulation of the cortical surface. However, the use of a stronger convulsant agent, ω-aminocaprylic acid (C_8), or of strychnine (35) does affect this response somewhat. Presumably, the relation of the cerebellar dendrites to the electrically excitable membrane of the neurons is somewhat different and such, that the non-propagating dendritic p.s.p.'s spread more effectively into the electrically excitable regions (15) of the cerebellum.

The same overtly excitatory action produced by blockade of inhibitory synapses could lead not only to spikes evoked by the already extant p.s.p.'s; in appropriate circumstances excitation of spikes could involve new components in the activating pathway and this could introduce new potentials at the cerebellar cortex, as has been demonstrated in the responses of cerebral cortex (36, 37). They might be spikes, but they might also be new p.s.p.'s. Such additional components are seen in two of the cases analyzed (Figs. 5 and 8). In both situations these additional potentials were produced late. However, only in the case of Fig. 8 was the added component of such magnitude as to alter markedly the character of the response (records *3* and *7*). In this situation the initial dendritic p.s.p.'s of both sign were nearly equal in magnitude, although occurring at different times. The new component of p.s.p. far outweighed all other potentials evoked in the system. It is perhaps noteworthy that the surface-positive reticulo-cerebellar activity contains masked components of negativity which become prominent during the activity cycle (Fig. 13). A similar relation is also found in reticulo-cerebral responses (23). In that case interactions of two stimuli disclosed a large positive component which was concealed in the surface-negative response to a single reticular stimulation.

The cerebellar hyperpolarizing dendritic p.s.p.'s usually developed markedly late in the total cortical response. The delays are considerable in electrophysiological terms (*e.g. ca.* 10 msec. in Fig. 7) and indicate a considerable difference in the organization of the paths which lead to the final effectors—in this case the excitatory and inhibitory dendritic synapses.

Another feature of the cerebellar activities is the presence, to various degrees in the different responses, of potentials that are not affected by either GABA or C_6. The smallest component of this kind was seen in the directly evoked activity (Fig. 5, record *2*). In most of the other responses analyzed in this paper this drug-resistant component was large and surface-positive, but in crus I (Fig. 6) it was surface-negative. These potentials may have several origins. They may derive from afferent fiber activity, and this is probably the nature of the relatively small, brief, diphasic potential remaining in the direct cortical response after the dendritic p.s.p.'s were eliminated by GABA (Fig. 5, record *2*). Another source of potentials could be the discharging

cells. The electrotonic spread of their activity might result in potentials of either sign, depending upon net distribution of current flows. Also, synaptic potentials in different portions of the neuron all might contribute to the electrotonic components. It is probably impossible to evaluate these sources either from surface recordings or from depth recordings of the generalized fields (*cf.* reference 15). On the other hand, analysis by sampling of individual units with external or internal microelectrodes is an arduous task that has not yet been carried out on a scale adequate to make correlations, or indeed, with the specific aims required by the present analysis.

The synaptic configurations activated by stimulating different peripheral nerves appear to be nearly identical (Fig. 8). However, the vermian cortex which receives most of the spinal projections (7, 17) responds with different synaptic patterns to stimuli from intracerebellar pathways. The responses to stimulating the fastigial nucleus (Fig. 4) resemble most closely those to peripheral stimuli (Figs. 2, 8, 9, and 11). In both there are large axosomatic components as well as some spikes. The axodendritic e.p.s.p. appears to be smaller in Fig. 4 (record *2*) and later. There is probably no dendritic i.p.s.p. Another pathway, from the anterior vermis to the caudal (records *5–8*), had only a small amount of axodendritic component, all of e.p.s.p., since the surface-positive potential broadened slightly on applying GABA (record *6*).

The paramedian lobule also responded differently to excitation by different pathways, as is seen from the effects of the drugs in the three experiments of Fig. 3. The inferior olivary stimulus produced relatively little p.s.p.'s after the early polyphasic sequence which is to be ascribed to spikes. The reticulocerebellar pathway, as already mentioned in connection with Fig. 13, sets into motion long lasting excitatory and inhibitory effects which determine the activity cycle. In the large positive conditioning response (Fig. 3 B) there are large components of dendritic e.p.s.p.'s, for GABA enhanced and prolonged the positivity. On the other hand, the three experiments involving excitation of the paramedian lobule, which are shown in Figs. 3 C, 5 and 10, produced markedly similar responses and these behaved similarly to application of drugs.

The changes that were induced by the drugs appear to have been mainly in that component of cerebellar activity which has been designated potential III (7). This is the chief activity induced in the cerebellar cortex by all the pathways and since it is large it is probably mainly due to discharge of Purkinje cells. This activity should involve a surface-positive component, the discharge of the cell bodies (33), and also the activation of their profuse dendritic arborization by various means (*cf.* references 2, 9, 19). Earlier activity, insensitive to the drugs, is seen in various figures (*e.g.* Fig. 2), but as the present work was concerned chiefly with the synaptic components, little attention was paid to the impulse in the afferent pathways and to the small intermedi-

ate potentials which are lumped in potentials I and II of the responses (7). Prominent contributions from these are seen in Fig. 3 A; Fig. 4, records *9–12*; and Fig. 7.

The electrophysiological data shown in Figs. 12 and 13 also fit in with the pharmacological analysis given here of the nature of cerebellar cortical potentials. In particular these data indicate that inhibitory processes do play a role in cerebellar cortical activity. These processes do not, however, contribute as prominently to the electrical activity recorded from the cerebellar cortex as they do to that in the cerebral cortex.

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