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CORTICAL CONTROL OF THE UNIT ACTIVITY IN NUCLEUS MEDIALIS DORSALIS THALAMI OF THE CAT

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Abstract. Effects of electrical stimulation of OFC (gyrus proreus, gyrus orbitalis, gyrus sigmoideus anterior) on MD unitary activity were studied. Acute preparations, curarized and unanesthetized or anesthetized with chloralose or barbiturates, were used. Steel microelectrodes were used for recording. Single rectangular pulses (0.5 msec and 0.1–0.5 ma) or short duration trains of stimuli were delivered. 479 neurons were tested and 244 (50.9%) responsive cells were revealed. Responses patterns: Type I, excitatory in nature. The discharge was composed of one or more spikes (latencies below 100 msec). Type II, characterized by the suppression or diminution of spontaneous activity during variable periods of time. Type III, defined by the appearance of burst activity (latencies above 150 msec). Values up to 1500–2000 msec were not rare. Type II and III responses have clearly prevailed. The g. proreus stimulation gave the higher MD responsive values. Successive stimulations of the five cortical areas were made to study convergence phenomena. The largest degree of convergence was found with stimulation interplay at the two zones of g. proreus. In a small group of neurons, the convergence of cortical and peripheral natural stimulation was also observed. A hypothesis has been proposed for long latency response generation and the inhibitory effect of cortical stimulation on the nuclear activity has been emphasized.

The reciprocal anatomic connections between the medialis dorsalis (MD) nucleus and the orbitofrontal cortex (OFC) have frequently been emphasized (Clark and Boggon 1933, Waller and Barris 1937, Walker 1940, 1959, Waller 1940, Freeman and Watts 1947, Rose and Woolsey 1948, 1949, Pribram et al. 1953, Akert 1964, Ajmone-Marsan 1965, Khalifeh et al. 1965, Wells 1966). The descending pathways originate in the

gyrus proreus (Auer 1956, Johnson et al. 1968, Rinvik 1968*a*) and in the gyrus orbitalis (Nauta 1964). The gyrus sigmoideus anterior also projects to MD (Rinvik 1968*b*). Murphy and Gellhorn (1945) and Niemer and Jimenez-Castellanos (1950) showed that these connections could also be demonstrated by physiological neuronography. The first question to be asked concerns the electrophysiological correlates of these main corticofugal pathways.

The influence of cortical electrical stimulation of the frontal pole upon thalamic activity has been previously investigated in the thalamocortical specific system (Amassian 1952, Ogden 1960, Iwama and Yamamoto 1961, Angel 1963, Andersen and Sears 1964, Andersen et al. 1964*a*, *b*, Nakamura and Schlag 1968, Dormont and Massion 1970). It therefore seemed worthwhile to compare the results of these studies with those obtained in the present study through activation of the OFC–MD projections.

The cortical areas stimulated in the present experiments are rather different in function. The g. sigmoideus anterior forms part of the primary motor cortex and the g. proreus and the g. orbitalis are related to certain behavioral regulations and autonomic functions (Bailey and Bremer 1938, Bailey and Sweet 1940, Sachs et al. 1949, Warren and Akert 1964, Brutkowski 1965, Encabo and Ruarte 1967, and other papers in this issue). The third objective was therefore to investigate whether all of these functionally different cortical areas control the MD activity similarly or in a manner specific for each area.

The MD unitary activity evoked by somatic or subcortical stimulation (Rudomin et al. 1965, Feltz et al. 1967, Encabo and Volkind 1968, Encabo and Bekerman 1971) offers some noteworthy features, particularly the long-latency responses of hundreds and even thousands milliseconds, which deserve special attention. It will be of some interest to shed further light upon the nature of these responses.

Finally, considering that somatic afferents to MD are already known, it might be of some value to investigate whether the frontal area modulates the peripheral input to the nucleus.

MATERIAL AND METHODS

Thirty-five adult cats were employed. Three different preparations (A, B, C) were made. In 10 animals (Series A) ether was used only for the surgical phase and anesthesia was discontinued during the experiment. The pressure and incision zones were carefully infiltrated with procaine. In Series B, 15 cats were anesthetized with chloralose (80 mg/kg i.v.) whereas in Series C (10 cats) barbiturate agents (Diabutal 30–40 mg/kg i.p.) were used.

All the animals were placed in a standard stereotaxic apparatus, immobilized with gallamine and artificially ventilated. Ipsilateral enucleation and removal of the posterosuperior wall of the orbit permitted an approach to the orbitofrontal cortex. The stimulating electrodes (bipolar) were fine metal threads isolated except at the tip.

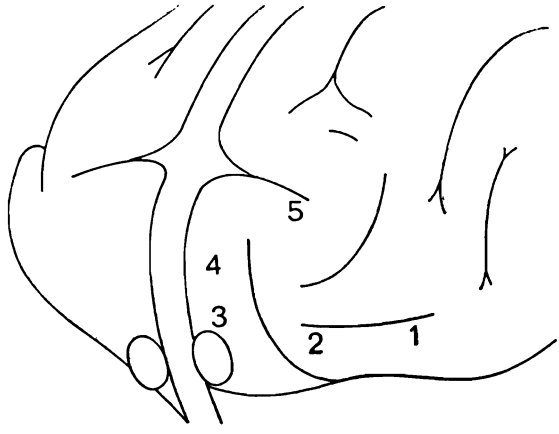


Fig. 1. Numbers in this Figure and subsequent ones indicate the site of stimulation: *1*, g. orbitalis (posterior part), *2*, g. orbitalis (anterior part), *3*, g. proreus (ventral part), *4*, g. proreus (dorsal part), *5*, g. sigmoideus anterior.

Five pairs of electrodes were placed as follows (Fig. 1): Electrodes *1* and *2* in the g. orbitalis in its posterior and anterior part respectively. Electrodes *3* and *4* in the ventral and dorsal portion of the g. proreus and Electrode *5* in the g. sigmoideus anterior. The stimuli were single rectangular pulses (0.5 msec, 0.1 to 0.5 ma) or short trains at frequencies of 200–300/sec directed by means of a stimulus isolation unit.

A dorsal approach was used for reaching the nucleus MD and the area studied was encompassed between the coordinates A8–10, L 0.5–2,5, H +5 – +2 of the Jasper and Ajmone-Marsan atlas (1954).

The extracellular electrical activity was recorded with steel microelectrodes (initial resistance of 10–20 MΩ) prepared according to Green's technique (1958).

The activity was fed to a 565 Tektronix CRO through a bioelectric neutralized capacity amplifier and a 122 Tektronix amplifier. The vertical signal out of the 565 Tektronix was connected to an Ampex SP 300 where the information was stored and from which, at a later time, the photographic images were taken.

The physiological condition of the preparation was controlled by monitoring rectal temperture, pupillary miosis, cortical vascularization and

electrocardiogram. The animal was allowed a period of at least 2 hr for recovery between surgery and the experimental phase.

At the end of the experiment, the brain was removed and fixed in formol. Histologic controls were obtained using Nissl's technique.

SPONTANEOUS UNITARY ACTIVITY IN THE NUCLEUS MEDIALIS DORSALIS

The MD spontaneous unit activity (Fig. 2) usually showed a pattern of randomly distributed single spikes (positive-negative of brief duration, 1–3 msec and variable amplitude 0.5–10 mv). On some occasions simultaneous records from 2 or 3 units (Fig. 4*B*, 6 and 11*A*) or from still more numerous units (Fig. 2*E* and 8*B*) were obtained.

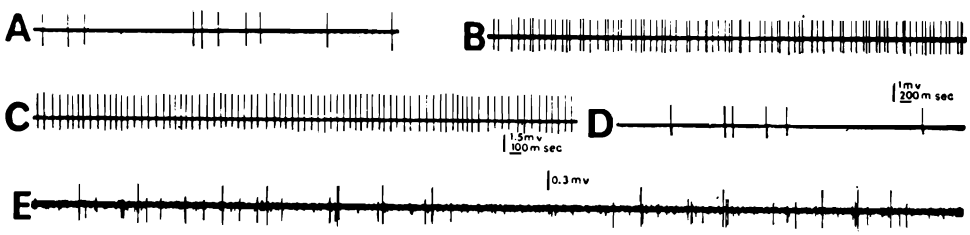


Fig. 2. Spontaneous activity. *A*, *B* and *C*: single spike discharge. *B*: barbiturate anesthesia, *C*: pacemaker-like activity. *D*, E: burst activity. *E*: multiple-unit discharges. Voltage calibration common to *A*, *B* and *D*. Time calibration common to *A*, *B*, *D* and *E*. Positivity is upwards here and in subsequent Figures.

In some cases, silent units were found which could only be triggered by stimulation (Fig. 3*ABC*, 4*B*, 6, 8*A*, 10*AB* and 11). These cells were more frequently found in chloralosed preparations.

It was not possible to detect any special pattern of spontaneous activity. It appeared as single spikes (Fig. 2*ABC*) or in bursts of two to five elements at frequencies of 150–300 per sec (Fig. 2*DE*). It was unusual to find a combination of both types in the same unit.

Schlag (1958) observed that with the use of barbiturate anesthesia, the spontaneous thalamic activity takes exclusively a burst pattern. In fact, a prevalence of this type of activity was seen in C preparations although non-burst spontaneous firing was also seen (Fig. 2*B* and 11*A*). An overdose of Diabutal changed likewise the unit spontaneous activity from isolated spikes into bursts. In addition, the predominance of activity was even more noticeable when it followed this overdose. This uniform burst activity found by Schlag might be explained by the fact that this author investigated the barbiturate effect immediately after the i.v. injection.

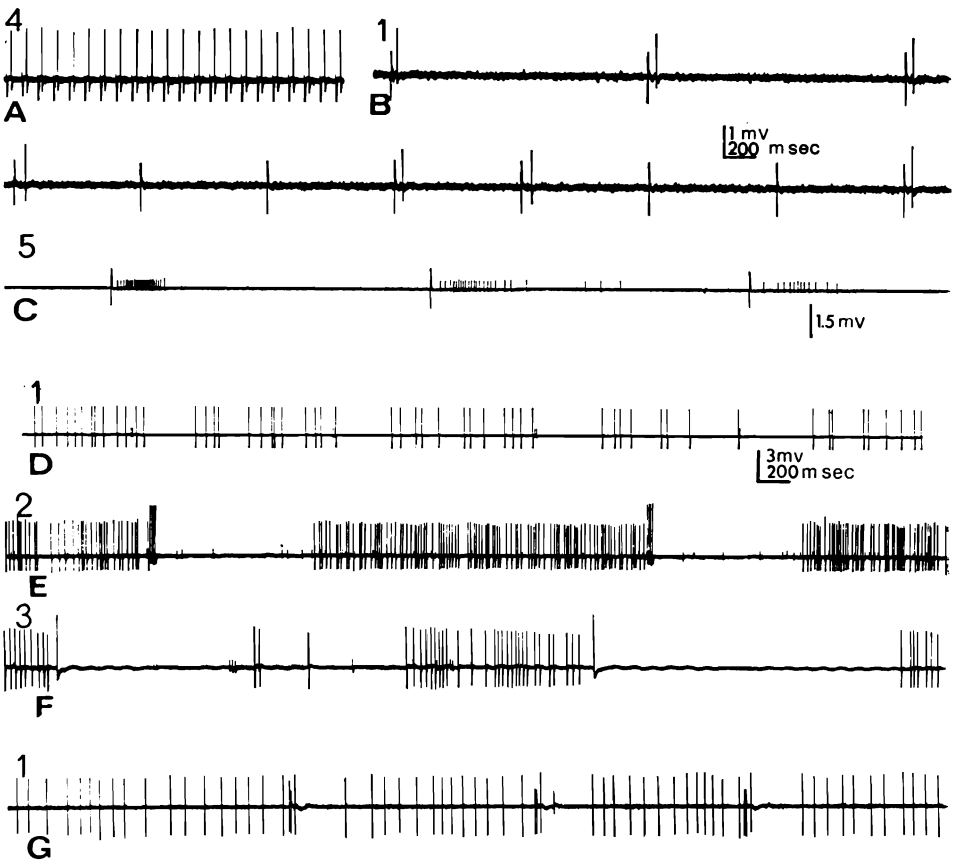


Fig. 3. Type I and Type II responses. *A*, *B* and *C*: Type I response. *A*: constant, single spike response. *B*: inconstant single spike discharge, the response being sometimes absent when the stimulation frequency is increased. *C*: response diminution with successive stimuli. Time calibration common to *A*, *B* and *C*. Voltage calibration common to *A* and *B*. *D*, *E* and *F*: Type II responses. The duration of the interval is 400–500 msec (*D*), 1000 msec (*E*) and 1500–2000 msec (*F*). *G*: association between Type I and Type II response. Time and voltage calibration common to all records.

NEURONAL RESPONSES TO CORTICAL ELECTRICAL STIMULATION

One undesirable aspect of the method employed is the simultaneous activation of both corticofugal and corticipetal fibers. The antidromic thalamocortical stimulation produces several effects which could mask the action of the corticothalamic fibers fired at the same time. To avoid this difficulty, low intensity electrical stimulation was employed and it can be assumed that the following description refers only to the orthodromic activation of corticothalamic fibers. The possible participation

of more complex circuits, depending on the other OFC efferent connections cannot be disregarded (Auer 1956, Rinvik 1968*ab*, Nauta, this Symposium).

A total of 479 neurons were studied. Responses were obtained in 244 units. Series A and B showed closely similar results, whereas the response values under barbiturate anesthesia were lower (Table I).

TABLE I

MD responses to cortical stimulation[a]

	Animals	Units tested	Responses
Non-anesthetized (Series A)	10	140	90 (64.3)
Chloralose (Series B)	15	161	105 (65.2)
Barbiturates (Series C)	10	178	49 (27.5)
total	35	479	244 (50.9)

a The percentage is given in brackets.

Type of responses

The three types of responses to be described have some features in common. Some cells maintained fairly constant responses (Fig. 3*A*). However, different variations, like changes in latency and duration, were frequently observed. Figure 4*B* is the simultaneous recording of two spontaneously silent units, the smaller one presenting a stable latency (1800 msec), whereas the larger varies between 2100 and 3300 msec. Such lability of responses (usually dependent on the stimulating frequency) was repeatedly seen (Fig. 3*BC*).

Type I response (Fig. 3*ABCG*). It was defined by the firing of a single spike, a group of them (not burstlike), or a long-lasting discharge. The latencies exceptionally attained 100 msec. A particular kind of this response was an acceleration of discharges in cells with very fast spontaneous activity, it was usually impossible to determine exactly either beginning or end of this kind of response.

Type II response (Fig. 3*DEFG*). In spontaneously active cells, a diminution of rates of discharge, or its suppression during variable periods of time (from 10 msec to 5 sec) characterized the Type II response. In Fig. 3*G* a unit is seen in which a Type I response was followed by a Type II response. This pattern was found only in four units in the present experiments.

Type III response (Fig. 4, 6, 7, 9, 10 and 11). This group includes the responses defined by the presence of one or several burst discharges. The burst response was quite similar to the spontaneous unitary activity described in preceding Section. When the spontaneous activity was absent or scarce, the burst response appeared as a purely excitatory phenomenon (Fig. 2*AB*, 6, 8*A*, 9, 10 and 11) and when the spontaneous activity was clearly present the burst responses were always preceded by a pause (Fig. 4*ACD*). This inhibitory effect looked superficially like the suppression phenomena in Type II responses.

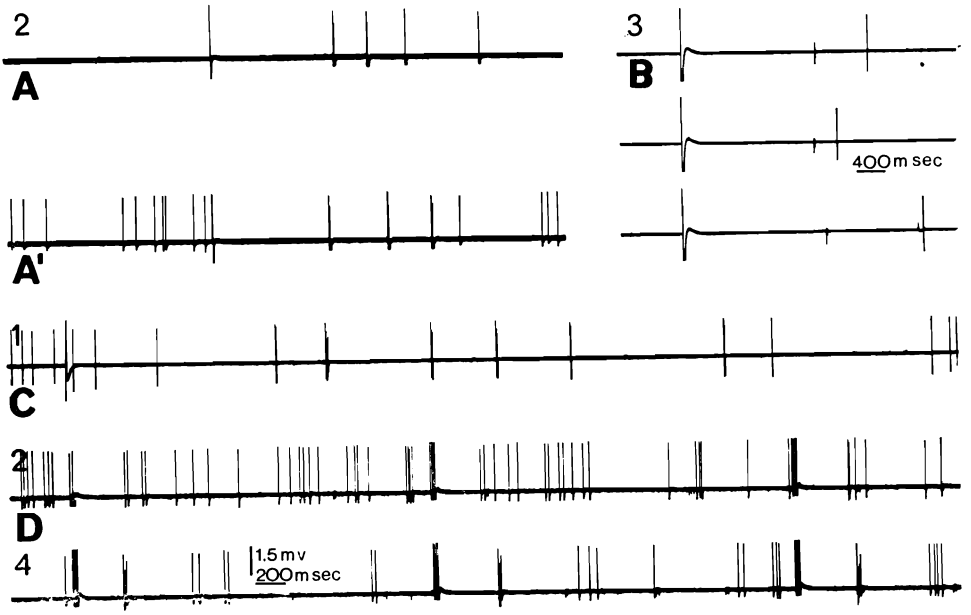


Fig. 4. Type III responses. *A*, *A'*: same cell, similar burst response. *A*: spontaneous activity is absent, *A'*: spontaneous activity being present, suppression can be observed. *B*: simultaneous recording from two neurons. The smaller has a fairly constant latency, the larger shows a wide range of latencies. *C*: long duration suppression and multiple-burst activity. Note that spontaneous activity is still present long after stimulation. *D*: same cell. Electrode *2* produces a Type II response. Electrode *4* evokes a Type III response. Voltage calibration is common to all records. Time calibration is common to *A*, *A'*, *C* and *D*.

As the frequency of the spontaneous activity increased, it was usually found that the number of burst discharges became greater. For Series C, the rule was that there were bursts even though spontaneous activity was scarce or absent.

In multiple burst responses, those following the first burst were very inconstant. The latencies were exceptionally below 100 msec.

From the above description, it should be understood that the frequent

association between an inhibitory effect (Type II response) and an excitatory burst discharge (Type III response) has been considered a Type III response.

Table II shows the distribution of response types according to the different sites of stimulation. Type III responses clearly prevailed.

TABLE II

Type of responses[a]

Stimulation		Units tested	Total	Type I	Type II	Type III
	A	139	52 (37.4)	9 (16.3)	7 (13.3)	38 (70.4)[b]
1	B	152	53 (34.9)	15 (28.3)	10 (18.9)	28 (52.8)
	C	178	13 (7.3)	2 (15.4)	1 (7.7)	10 (76.9)
	A	139	39 (28.1)	4 (10.2)	12 (30.8)	23 (59.0)
2	B	153	41 (26.8)	11 (26.8)	6 (14.7)	24 (58.5)
	C	178	15 (8.4)	6 (40.0)	1 (6.7)	8 (53.3)
	A	139	64 (46.0)	7 (10.5)	9 (13.4)	51 (76.1)[b]
3	B	153	68 (44.4)	16 (23.5)	13 (19.1)	39 (57.4)
	C	178	30 (16.9)	2 (6.7)	2 (6.7)	26 (86.6)
	A	137	74 (54.0)	6 (8.0)	9 (12.0)	60 (80.0)[b]
4	B	152	67 (44.1)	15 (22.4)	11 (16.4)	41 (61.2)
	C	177	27 (15.3)	0 (0.0)	1 (3.7)	26 (96.3)
	A	136	30 (22.1)	6 (20.0)	8 (26.7)	16 (53.3)
5	B	152	32 (21.1)	8 (25.0)	3 (9.4)	21 (65.6)
	C	177	10 (5.6)	0 (0.0)	1 (10.0)	9 (90.0)

a The percentage is given in brackets.

b Type I and II, or Type I and III responses were simultaneously present. Therefore the sum of Type I, II, and III responses exceeds the total number of responsive units.

In Fig. 5, latency histograms corresponding to Type I and III responses for each of the five stimulating electrodes have been presented. Since it was not possible to demonstrate statistical differences among the latencies of the three preparations used (A, B, C), the histograms were made by grouping all of the values together. In the largest histogram, the latencies of all responses obtained by the stimulation of the five electrodes were put together. The abscissae indicate the latencies in milliseconds. A logarithmic scale was used because the values, particularly those for Type III repsonses, tended to fall into a log-normal distribution. The ordinates indicate the number of observations.

Each observation is the latency determination for a single cell from stimulation by one electrode, therefore the same unit might be repre-

sented in more than one histogram. White and black surfaces correspond to Type I and Type III responses respectively. The geometric mean is indicated together with the limits of the confidence interval ($p = 0.05$) showing differences between the two types of response (in brackets). The values for each stimulating electrode are given in Table III.

TABLE III

Latencies; mean values (in msec) and limits of the confidence intervals ($p = 0.05$)

Cortical stimulation	Type I responses		Type III responses	
	$\bar{x}$	C I	$\bar{x}$	C I
1	33	(31–35)	417	(363–480)
2	34	(29–44)	423	(369–486)
3	28	(18–42)	485	(432–544)
4	29	(22–40)	490	(437–550)
5	36	(24–53)	429	(346–533)

SIGNIFICANCE OF THE DIFFERENT TYPES OF RESPONSES

The antidromic stimulation has been repeatedly used to study VB and VL thalamic activity (Andersen and Sears 1964, Andersen et al. 1964*ab*, Nakamura and Schlag 1968, Dormont and Massion 1970). Before considering the nature and physiological significance of the three types of responses, it must be explained why antidromic activity was ruled out in these experiments. According to Wolstencroft (1964), three criteria identify an antidromic response: (i) Short and constant latencies. (ii) The response capacity of the neuron to follow high frequency repetitive stimulation (50/sec or more). (iii) Cancellation of antidromic potential by a preceding orthodromic spike. This last technique has not been employed in this series. Type I responses were the only ones to be included in the discussion of these criteria, although their latencies were always above the antidromic response values. However, unusually long latency antidromic responses (12-34 msec) have been reported (Novin et al. 1970, Sundsten et al. 1970) in the para-ventriculo-hypophyseal system distinguished by its extremely thin fibers. Sixteen out of more than 100 Type I responses had latencies around 30 msec and therefore might eventually be considered as antidromic. Nevertheless, they represent a small group in the total number of responses. The lack of antidromic responses could be due to the low stimulation intensity (probably below the threshold for the axonal endings). In fact, the authors already mentioned have used higher stimulation parameters for successful antidromic activation.

Type I responses

If the 16 units, which might be suspected of antidromic activity, are discarded, the remaining Type I responses must represent the excitatory effects of corticothalamic firing. One may ask whether the connections revealed by stimulation are monosynaptic or polysynaptic. Unfortunately no definite answer is available. The latencies were higher than those currently accepted for monosynaptic responses (Fig. 5, Ta-

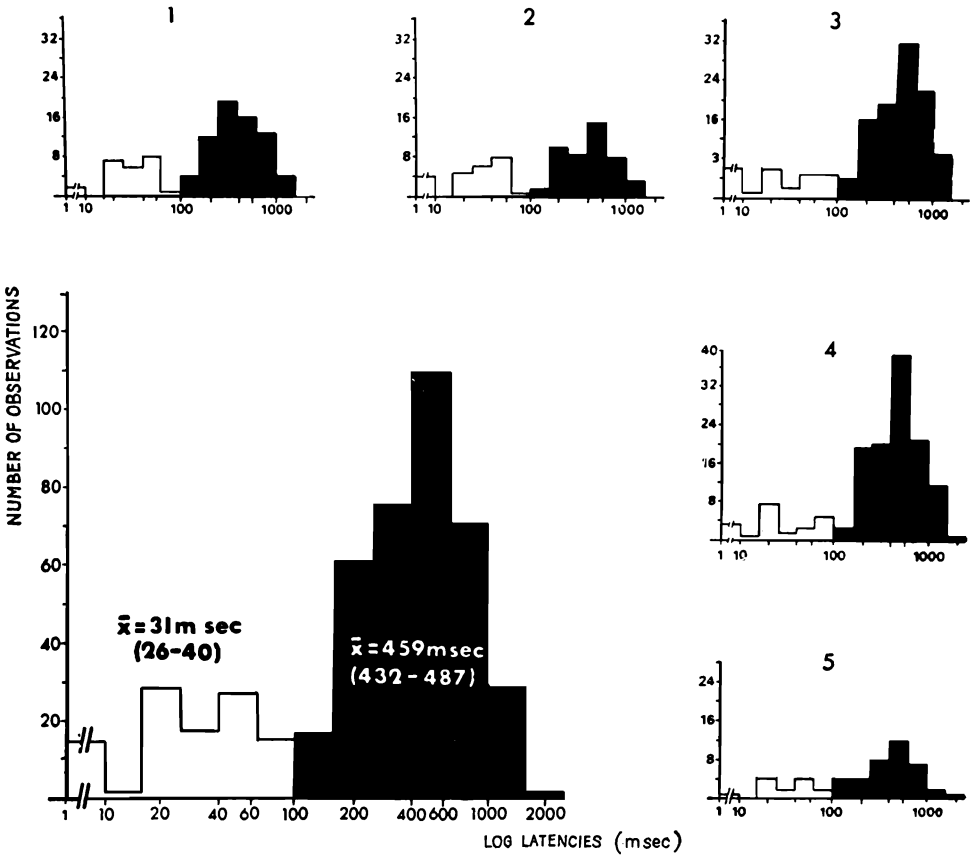


Fig. 5. Latency histograms. For explanations *see* text.

ble III). However, the corticothalamic fibers are extremely thin and therefore their conduction velocity must be very low (Rinvik 1968*a*). In fact, Ishikawa et al. (1966) and Sundsten et al. (1970) have reported conduction velocities of about 0.7 m/sec in the hypothalamus of the cat.

Type II and Type III responses

The presence of an inhibitory phenomenon could clearly be seen in Type II responses, if inhibition is used in the broad sense of a suppression of spontaneous discharges. Such a merely descriptive usage excludes any concommitant regarding the nature of inhibition, which cannot be determined from extracellular recording alone.

When Type III responses appeared in units with spontaneous activity, they were associated with inhibition of this discharge (Fig. 4*A'CD*). In this case, too, there was an inhibitory phenomenon. The intracellular studies at thalamic levels (Andersen et al. 1964*a,b*; Andersen and Sears 1964, Nakamura and Schlag 1968, Dormont and Massion 1970) have proved that the spontaneous activity is stopped by the development of a long-lasting hyperpolarizing potential (IPSP). The burst response is fundamentally due to a repetitive cellular discharge occurring in the Post Anodis Exaltation State (PAE) in the IPSP decay phase (rebound discharge).

In spontaneously silent units, Type III responses were seen but the inhibitory phenomenon could not be disclosed from extracellulary recording. In Fig. 4*AA'* a single cell shows the same burst responses, in *A* the neuron was silent and in *A'* it showed spontaneous activity. An additional argument in favor of the inhibitory nature of this process is given in Fig. 6, where as already shown by Albe-Fessard and Kruger (1962), the increase in stimulus strength had probably lengthened the IPSP and therefore the latency of the burst discharge as well. One can therefore postulate an identical mechanism for all of the burst responses — namely a rebound discharge following IPSP's of long duration.

The responses are divided into two groups (Type II and III), even though they both could correspond to an inhibitory mechanism because, on the one hand, it is not possible to be sure whether or not some other inhibitory processes are involved (e.g., presynaptic inhibition) and on the other hand, by the presence of the burst activity itself. In fact the burst discharge seems not to depend only on a phenomenon of PAE. Andersen and Sears (1964) argue that a special depolarizing potential is necessary to generate a rebound discharge in addition to the restoration of the membrane potential, Albe-Fessard and Kruger (1962) proposed, in addition to the PAE, tre arrival of very slowly conducted impulses, and Nakamura and Schlag (1968) stated that "PAS facilitates excitatory processes rather than trigger the discharge itself".

In Fig. 4*D*, a cell can be observed which responds with a purely inhibitory effect to stimulation by Electrode *2* and then changes to a Type III burst response when Electrode *4* is activated. This Figure suggests that burst activity is not random, since the inhibition is common to both

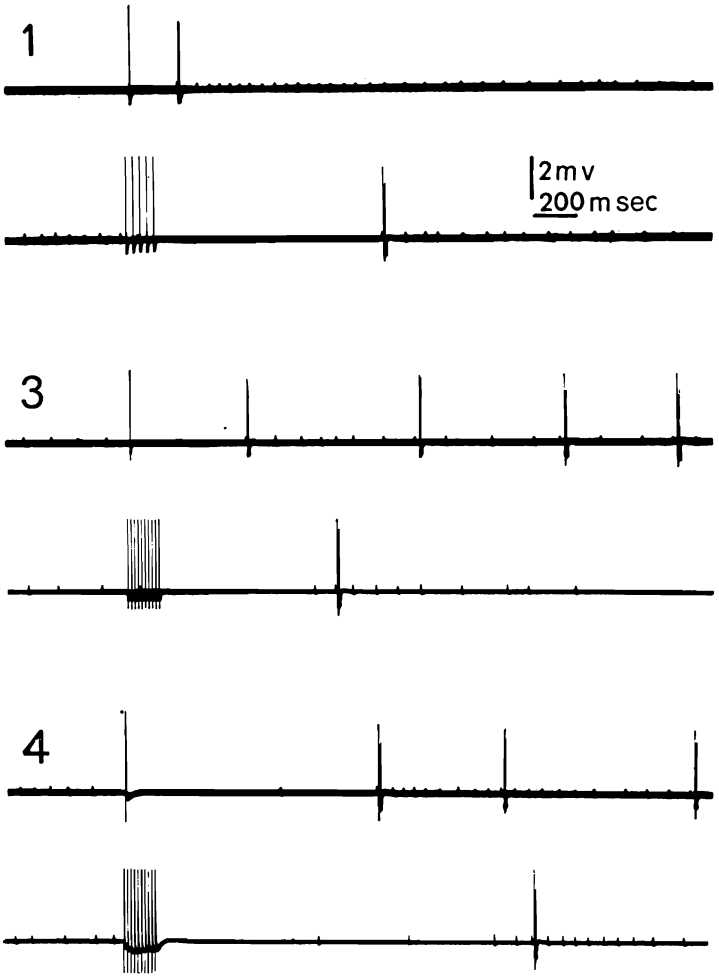


Fig. 6. Latency lengthening. The same cell increases its latency to stimulation by Electrodes *1*, *3* and *4* when, instead of a single stimulus, trains of impulses are delivered. Note also the suppression of discharges in the smaller spontaneously active cell.

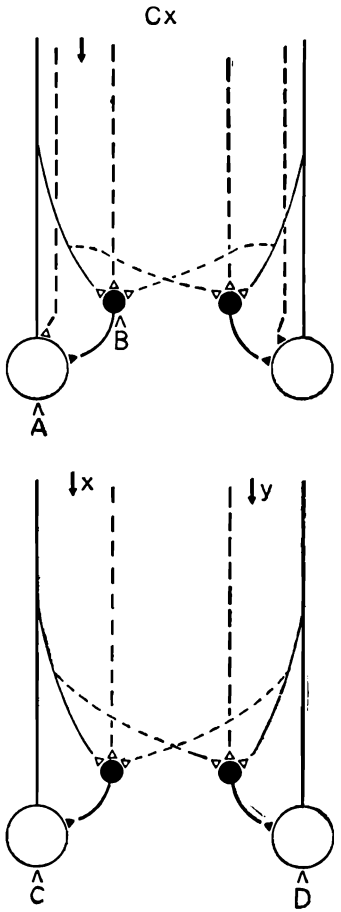
electrodes but the burst discharge follows the stimulation of only one of them. Andersen and Sears (1964) have stated that inhibitory responses may appear as a series of IPSPs and rebound discharge could be observed only after five or six IPSPs (the long latency Type III response of the present experiments). It can be assumed that in addition to PAE (present in the decay of every IPSP), there must be some other component, not yet identified, for eleciting the burst activity. This is an attractive hypothesis since thalamocortical rebound discharge could then be understood as an active process, instead of making it depend only on passive recovery.

SCHEMATIC OUTLINE OF THE OFC–MD SYSTEM ORGANIZATION

Figure 7 outlines a possible system of connections including some well settled features and some others not proved as yet. The corticothalamic and thalamocortical connections are drawn at the left. At the MD level, two cell types are included. The thalamocortical projection neuron (large and open circles) and the inhibitory interneuron (small and black circles) are drawn. The relationships described by Andersen and Sears (1964) are also represented: the recurrent axon collateral (open triangles) that stimulates the interneurons, and these in turn with their inhibitory effects (black triangles) upon the projection system. Filled lines were used for this well-known scheme. The broken lines are proposed to explain the results presented. Type II and III responses could arise in the projection cells. Type I response might be the cortical excitatory effect, evoked polysynaptically or monosynaptically, in an inhibitory interneuron. Type II and III responses will be consequently produced. To the right of the diagram, several response patterns are outlined. With recording electrode in *A*, the suppression effect is observed with or without burst response almost immediately after stimulation (upper rows) or with some latency (lower rows). With the recording electrode in *A* or *B*, an excitatory response is also shown.

Most of the results have a ready explanation, but there are some facts which deserve special attention. Seven units showed Type I and II responses (Fig. 3*G*), or Type I and III responses to stimulation by the same electrode. Another eight units gave Type I responses to stimulation by one electrode and Type II or III responses to stimulation of another site. There still is the possibility that the projection neuron could receive an excitatory cortical input. On the other hand, it cannot be ruled out that an almost immediate suppression of spontaneous activity (Fig. 3*E*) might be due to stimulation of a hypothetical inhibitory cortico-thalamic neuron (in this connection, it must be emphasized that no Type I responses with less than 5 msec latency were found). For the VB nucleus, Iwama and Yamamoto (1961) and Ogden (1960) have reported such an excitatory-inhibitory corticothalamic system. Amassian (1952) and Angel (1963) have underlined the inhibitory cortical control upon thalamic VB neurons, and Nakamura, Goldberg and Clemente (1967) showed an inhibitory effect on the masseteric reflex elicited by orbitocortical stimulation. In line with these earlier studies the present data corroborate the powerful inhibitory effect of OFC stimulation. An excitatory effect could also be revealed.

Upon studying the Type III responses, latency values were found which frequently surpassed 500 msec and occasionally attained 1500 and 2000 msec. Similar observations have been previously reported (Albe-



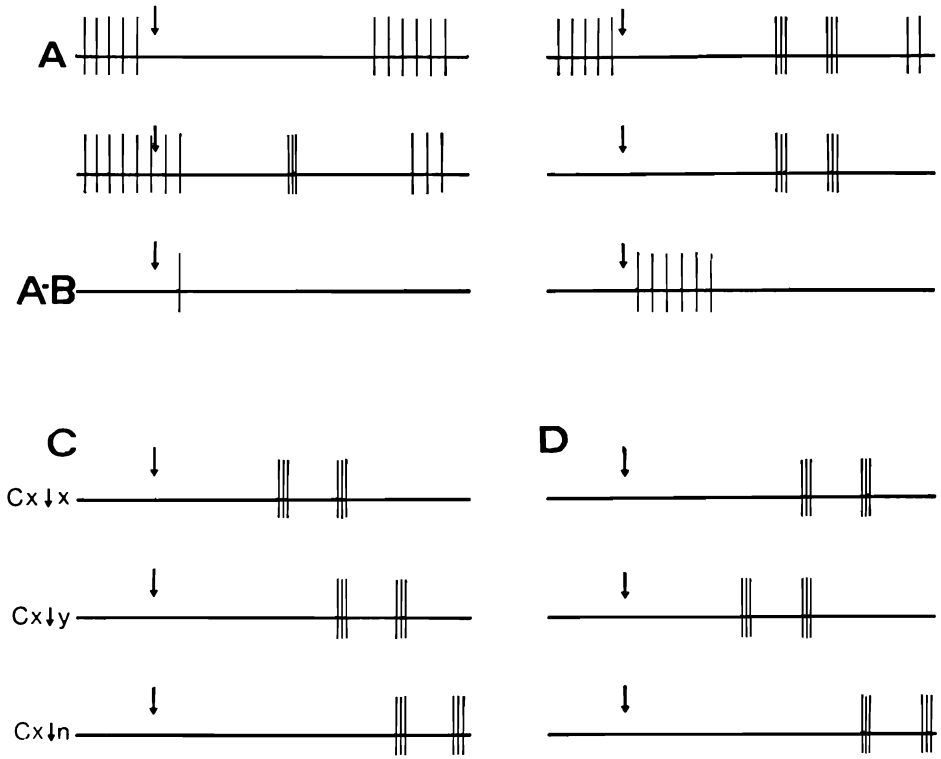


Fig. 7. A diagram of OFC → MD interaction (*see* text).

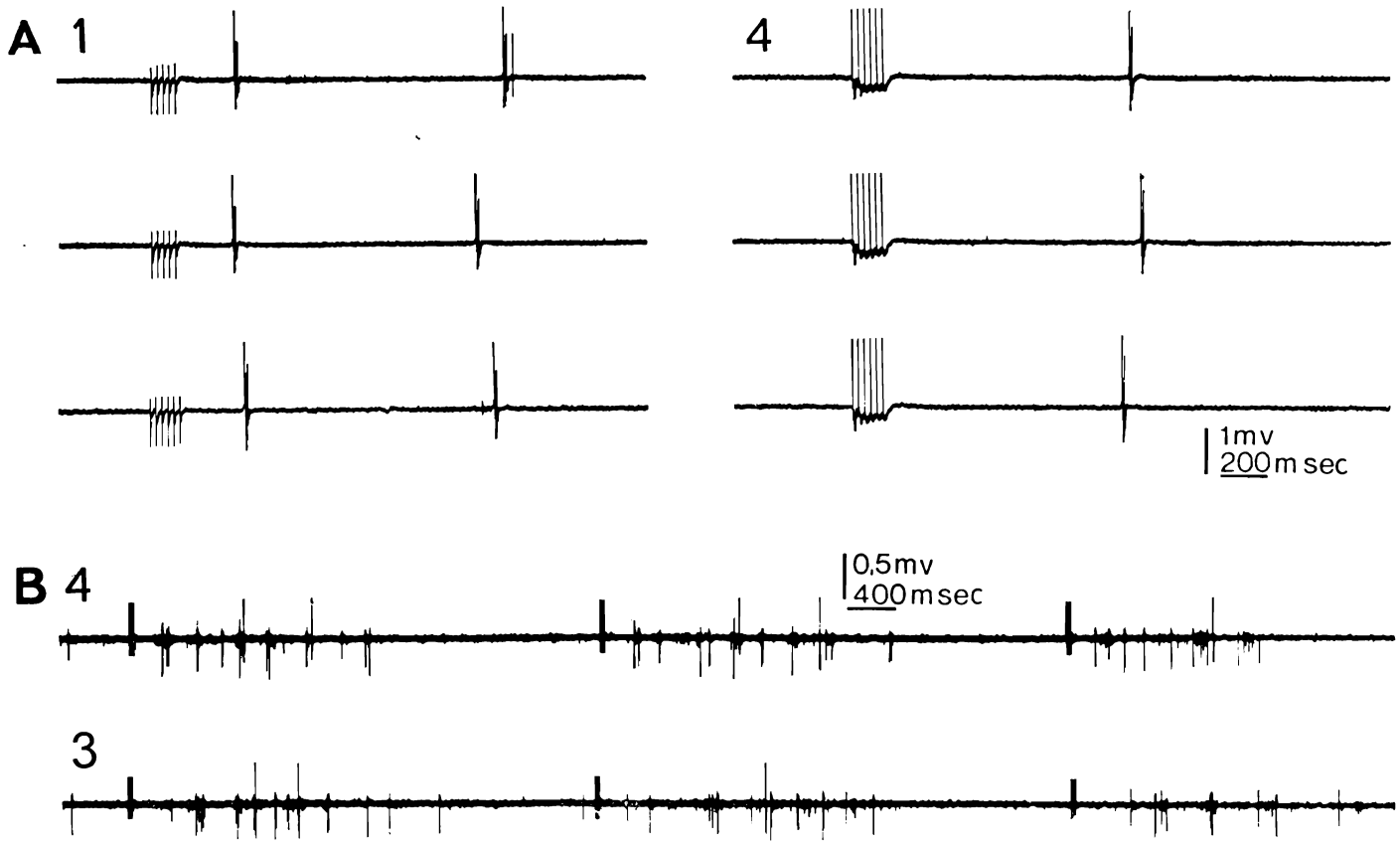


Fig. 8. *A*: Burst responses with different latencies depending on the site of stimulation. *B*: Multiple-unit recording. The responses of individual units have quite different latencies. The general response patterns vary with the stimulating electrode.

Fessard and Kruger 1962, Encabo and Volkind 1968, Nakamura and Schlag 1968, Dormont and Massion 1970, Encabo and Bekerman 1971).

Figure 7 suggests how such a long latency response might arise. The cortical stimulation of a particular point (*x*) produces at thalamic level (*C*) a Type III burst response at, say, 200 msec latency. If the cortical stimulation is delivered at another site (*y*), the burst response (always at *C*) increases its latency to 400 msec, the delay being produced as a consequence of the new cell involved with its burst response and recurrent collateral activation (broken lines). The same neuron fires with different latencies depending on the different sites of stimulation. The burst response of Type III is produced in one case by a neuron under "first-order recruitment" and in the other by the same cell but under "second-order recruitment". A different cortical stimulation area (*n*) can give still longer latencies.

Figure 8 presents the experimental results. In *A*, the response is produced at 400 msec latency by the stimulation through Electrode *1* whereas the latency for the activation by Electrode *4* was evidently increased. In *B*, the same phenomenon was registered. The multiple-unit record discloses several units activated with different latencies by stimulation of Electrodes *4* and *3*, suggesting that neurons under different kinds of recruitment were firing together. Finally, it should be remembered that some other processes could be participating as well, such as a very long IPSP (reported by Dormont and Massion 1970), or, possibly, negative feedback mechanisms aroused by n. reticularis thalami (*see* Scheibel and Scheibel 1966, 1967), or some other mechanisms, as yet undefined.

CONVERGENCE

In 214 responsive neurons convergence was investigated. In every case in this group, the five stimulating electrodes were tested. Two types of units were encountered: (i) those responding to stimulation by a single cortical electrode (46 cells, nonconvergent, restriced), and, (ii) those responding to stimulation by two or more electrodes (168 neurons, convergent, wide-spread). Table IV presents the results according to the three preparations used. The prevalence of convergence and the outstanding effect of anesthesia should be pointed out. Chloralose and barbiturates proportionately increased the nonconvergent groups.

Neurons responding to all 5 electrodes were scarce (Fig. 9). It was more usual to find responses to 2 or 3 electrodes, in combinations, in which the electrodes of the g. proreus were usually included. Therefore, in the cells responding to 2 electrodes, the more frequent combination was 3–4 (63, 55 and 69% for Series A, B and C respectively). The most

TABLE IV

Convergence[a]

Preparation	Nonconvergent	Convergent	Total
A	4 (4.9)	78 (95.1)	82
B	24 (28.9)	59 (71.1)	83
C	18 (36.7)	31 (63.3)	49
Total	46 (21.5)	168 (78.5)	214

a The percentage is given in brackets.

common associations for cells with convergence of 3 electrodes were *1–3–4* and *3–4–5*, and for 4 electrodes *1–2–3–4*. The percentage of neurons in which the 3–4 combination was present as compared with the total number of convergent units was 78% for Series A, 74% for Series B, and 70% for the Series C.

The 214 cells tested were also studied from a different point of view in an attempt to clarify whether some relationship could be established between convergent and nonconvergent groups on the one hand, and the type of responses on the other hand. Usually the convergent cells had similar types of responses for stimulation by different electrodes. The association between Type II and Type III responses was also not infrequent. Table V was made after excluding the eight cells showing the rare association of Type I and Type II (or Type III) responses. The Table reveals that the majority of Type I responses belong to the nonconvergent group and also that convergent pathways were preferentially used by impulses leading to Type II and III responses.

TABLE V

Convergence and type of responses[a]

Preparation	Responses Type I			Responses Type II and III		
	Nonconvergent	Convergent	Total	Nonconvergent	Convergent	Total
A	0 (0.0)	1 (100.0)	1	4 (5.1)	74 (94.9)	78
B	14 (70.0)	6 (30.0)	20	10 (16.7)	50 (83.3)	60
C	6 (75.0)	2 (25.0)	8	12 (30.8)	27 (69.2)	39
Total	20 (69.0)	9 (31.0)	29	26 (14.7)	151 (85.3)	177

a The percentage is given in brackets.

A hypothesis could be proposed on the basis of the experimental data and the previous studies of many other authors. Frequently the relationship between thalamic spindles and burst discharges of thalamic neurons

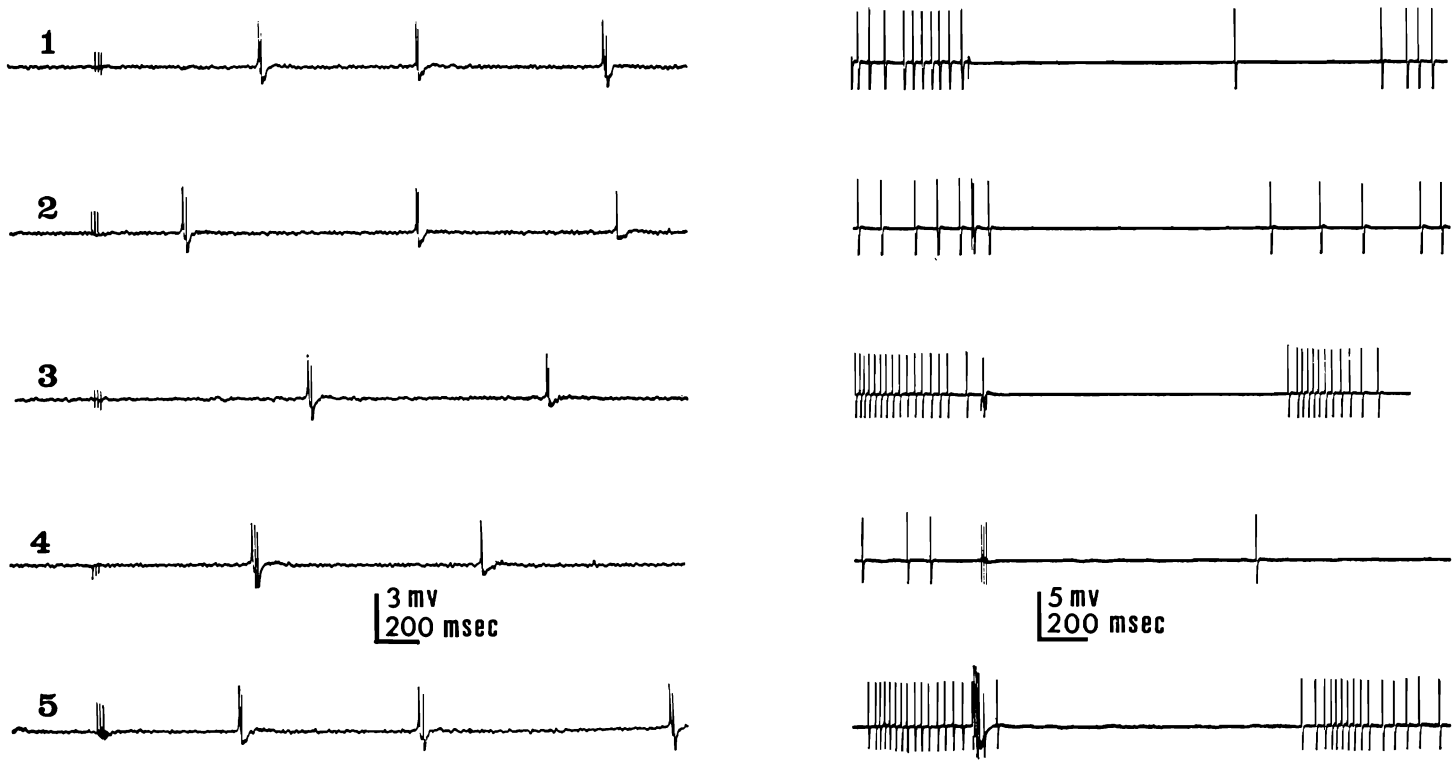


Fig. 9. Convergence. The five electrodes were effective for the two cells. Left: Type III response. Right: Type II response.

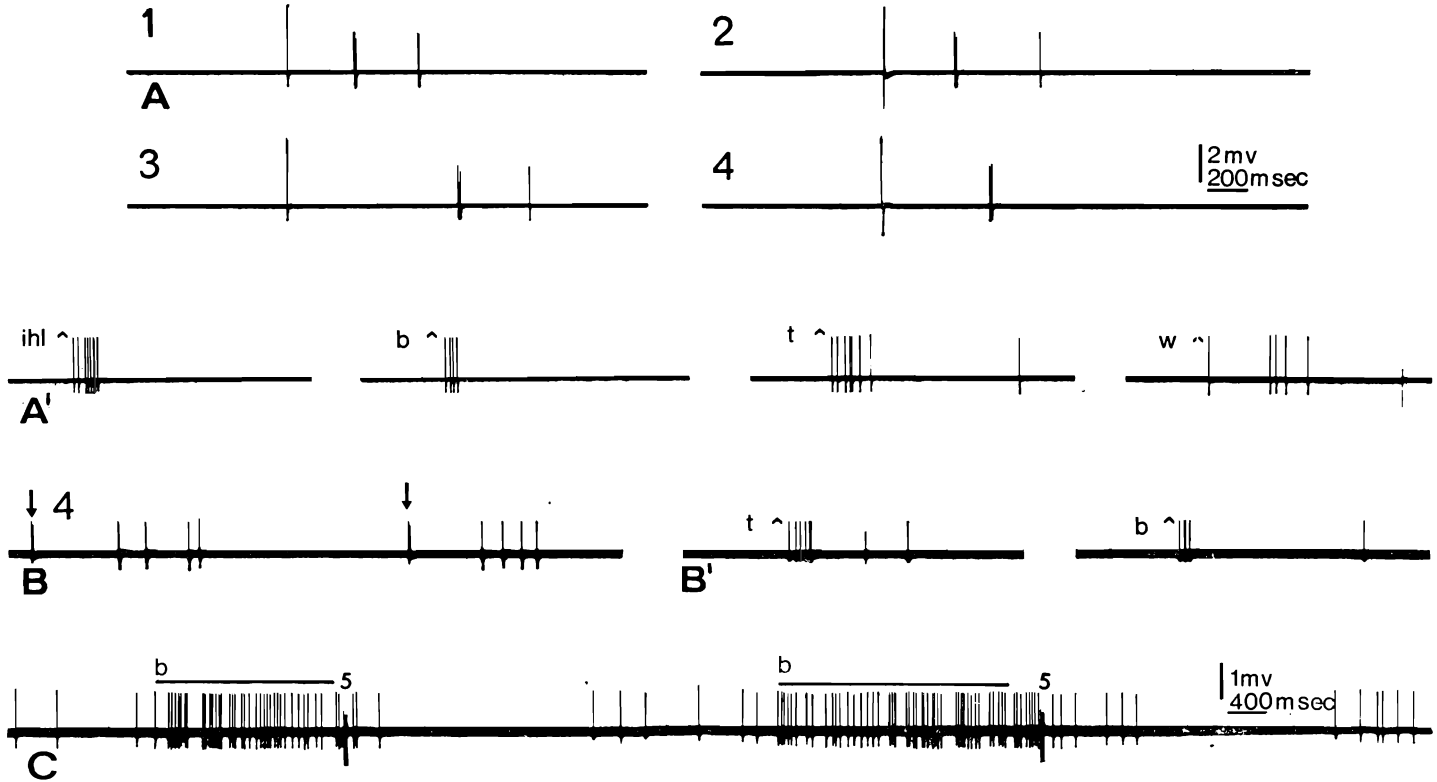


Fig. 10. Somatic and cortical convergence. *A*, *A'*: same cell. *A*: Type III responses to four cortical sites. *A'*: somatic responses. ihl: ipsilateral hind limb, b: body, t: tail, w: whisker. *B*, *B'*: another cell, barbiturate preparation. Similar effect. Calibration common to *A*, *A'*, B and *B'*. *C*: interaction between a continuous body stimulation and a cortical one.

has been emphasized (Verzeano and Calma 1954, Verzeano et al. 1955, Andersen and Sears 1964), and Andersen and Sears (1964) demonstrated that the spindle is composed of a group of several inhibitory potentials self-maintained by a feedback mechanism (the rebound-burst discharges). The predominance of convergence in units with Type III burst response is compatible with the idea that an important effect of frontal cortical stimulation at the MD level is the generation of spindles. The spindle (a phenomenon where cell populations and not isolated units are involved) requires a self-sustained recruiting mechanism of the type already described, possibly activated from different cortical regions through convergent fiber systems. However, in the study of convergence, it should be kept in mind that mechanisms of electrotonic spread of stimulation as well as corticocortical association could also be present.

Though not extensively investigated, the somatic and cortical convergence was also studied. In Fig. 10 *AA'* a convergent cell is shown with a widespread stimulation field: four cortical areas were active (with Type III response) with several tactile somatic stimuli added to them (with a quite different response pattern). Similar findings can be observed in Fig. 10 *BB'* in a barbiturized preparation. Somatic and cortical interaction was also disclosed. Figure 10 *C* demonstrates the suppression effect of the cortical activation upon the long discharge evoked by sustained tactile body stimulation. According to these data, MD somatic input (Rudomin et al. 1965, Feltz et al. 1967, Encabo and Volkind 1968) would be controlled by OFC activation. Furthermore, in the few cells observed (additional experiments are needed) the mechanism of modulation seemed to be purely inhibitory.

COMPARATIVE STUDIES AMONG DIFFERENT OFC AREAS

The five cortical regions under study were not equally effective. The responsiveness of MD neurons was most directly influenced by g. proreus stimulation. Table II summarizes these results. Electrodes *3* and *4* gave the higher values, whereas the g. sigmoideus anterior stimulation was less effective. Intermediate values were obtained for g. orbitalis activation. It should be pointed out that in Series C, despite the lower percentage of responses, there is a similar relationship among the three areas stimulated. No distinct response patterns were recorded in relation to particular cortical areas. The only differences found were the quantitative variations already mentioned.

The topographic distribution of responses through the entire MD was not thoroughly investigated — usually more units appeared in the ventral levels of the nucleus and therefore more responses were obtained in this area.

ANESTHETIC EFFECTS

Chloralose anesthesia confirmed some previous data (Kruger and Albe-Fessard 1960, Albe-Fessard and Kruger 1962, Albe-Fessard and Fessard 1963, Encabo and Volkind 1968) i.e. an over-all decrease of spontaneous activity and an increase of responses in silent cells. The Chi-square test was used to compare total number of responses between the A and B Series. No significant differences could be demonstrated. On the other hand with the same test ($p = 0.05$) it was shown that more Type I responses were found in chloralosed animals.

Barbiturates acted in a very specific fashion. Their effect was already seen in the increase of spontaneous burst activity. A dramatic reduction of response percentages (Table II) and an increase of Type III response (tested by Chi-square) were disclosed.

The following experiments carried out in barbiturized preparations complement the previous data. (i) Six units with fairly constant responses changed their pattern of activity to that of nonresponsive cells when the cat was overanesthetized (10 mg/kg i.v.), demonstrating the disappearance of responses 3–5 min after injection. In one case, the spontaneous activity also changed to a burst pattern. (ii) In 20 cells studied under deep Diabutal anesthesia, no responses were detected.

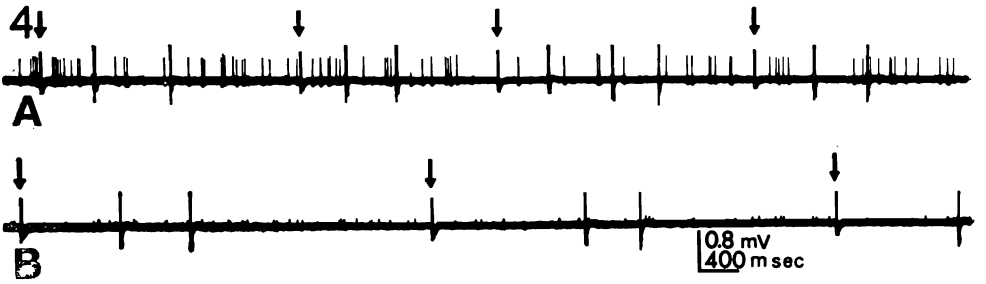


Fig. 11. Effect of barbiturates. *A*, before, *B*, after i. v. injection. Lengthening of latency of burst response.

Figure 11 shows the results of i.v. barbiturate injection. Two different cells are shown. In *A* and *B* (after Diabutal), activity in one disappeared and the other clearly increased the latency of its burst response. Barbiturate action of the OFC–MD system may be characterized in two ways — a reduction of total number of responses related to the general depressive effect of the barbiturates at the CNS level (Beecher et al. 1939, Larrabee and Posternak 1952, Verzeano et al. 1955, Valdman 1967) and a possible increase of inhibitory processes (increase of both spontaneous burst activity and burst Type III response).

CONCLUSIONS

Evidence has been presented that strongly suggests an OFC control over the MD neuronal activity. All the OFC areas have been successfully stimulated, as indicated by modification of MD neural discharges, and only quantitative differences were disclosed among them. The g. proreus stimulation evoked the largest number of MD responses.

A definite cortical inhibitory system has been proposed. It was disclosed with extracellular records in acute animals. Similar resuts were obtained with other methods and different preparations. On reporting these studies, Brutkowski stated in 1965 that — "analysis of behaviour changes in animals with frontal lesions reveals that the prefrontal cortex is essential for important inhibitory capacities". The attempt was made to account for the long-latency responses in the MD nucleus, and for their relationship with inhibitory processes, and particular cellular organizations.

Finally, a cortical modulation of MD somatic peripheral input was suggested.

SUMMARY

The effect of ipsilateral electrical stimulation of OFC (g. proreus, g. orbitalis, g. sigmoideus anterior) on MD unit activity was studied. Thirty-five adult cats were employed. Acute preparations — curarized and unanesthetized (Series A), or anesthetized with chloralose (Series B), or barbiturates (Series C), were used. In Series A, ether was needed only during surgery, and incision and pressure areas carefully infiltrated with procaine. Steel microelectrodes were used for recording. Electrical stimulation was delivered by single rectangular pulses or short duration trains of stimuli. The stimulation parameters were 0.5 msec and 0.1–0.5 ma, in an effort to avoid antidromic activation of thalamocortical fibers.

Spontaneous activity did not show any predominant patterns. A total of 479 neurons was tested and 244 (50.9%) responsive cells were revealed (64.3, 65.2, and 27.5% for Series A, B and C, respectively).

The following types of responses were described: Type I, excitatory in nature. The discharge was composed of one or more spikes with latencies below 100 msec. Type II, characterized by the suppression or diminution of spontaneous activity during variable periods of time. Type III, defined by the appearance of burst activity at latencies always above 150 msec. Values up to 1500–2000 msec were not rare. Type II and III responses were clearly predominant.

Forty-five per cent of the cells belonging to Series A and B responded to g. proreus stimulation. In series C, the responses diminished to

16%. The values for the stimulation of g. orbitalis were 30% for Series A and B and 8% for Series C. The stimulation of gyrus sigmoideus anterior gave the lowest values: 22% for A and B, and 6% for C.

Effects of successive stimulation at several or all of the five cortical sites were made to study convergence phenomena. Among 82 responsive neurons tested (Series A), 95% responded to stimulation of at least two different loci. For Series B, the values were 83 cells tested and 71% positive results, while for Series C 49 units gave 63% convergense. The largest degree of convergence was found with stimulation interplay at the two zones of g. proreus. In a small group of neurons, the convergence of cortical and peripheral natural stimulation was also observed.

A hypothesis has been proposed for long latency response generation and the inhibitory effect of cortical stimulation on the nuclear activity has been emphasized.

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