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Frontal Cortex Stimulation Evoked Neostriatal Potentials in Rats: Intracellular and Extracellular Analysis

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RYAN, L. J., J. M. TEPPER, S. J. YOUNG AND P. M. GROVES. *Frontal cortex stimulation evoked neostriatal potentials in rats: Intracellular and extracellular analysis.* BRAIN RES BULL 17(6) 751–758, 1986.—Evoked potentials, action potentials and intracellular events were recorded in the neostriatum of urethane anesthetized rats to electrical stimulation of frontal cortex white matter, motor cortex and pre-limbic cortex. Five major waves of the evoked potential were identified. Wave N1 (3.9 msec latency) was small, preceded cellular events and probably represents activation of corticostriate terminals. Wave P1 (10.8 msec latency to peak following white matter stimulation) coincided with an EPSP and neuronal firing. Both wave N2 (38.0 msec latency to peak) and P2 (approximately 110 msec duration) overlapped the intracellularly recorded hyperpolarization and inhibition of cell firing. Based upon this correspondence and upon the behavior of waves N2 and P2 with changing current and during conditioning-test paired pulse stimulation, it was concluded that the waves represent different processes contributing to the cellular hyperpolarization. A late wave, N3 (175 msec onset latency) corresponded to a late rebound firing and cellular depolarization. This late wave was eliminated from the neostriatum, but not from the overlying sensorimotor cortex, by kainic acid lesions that destroyed medial thalamus but left thalamic lateral nuclei and reticular nucleus intact.

Neostriatum Frontal cortex Medial thalamus EPSP Evoked potentials IPSP Basal ganglia

THE neostriatum is densely innervated by afferents arising from much of the cerebral cortex [5, 6, 8, 25]. These projections form primarily axo-spinous synapses within the neostriatum [4, 9, 20] and are believed to be strongly excitatory [3,11].

Electrical stimulation of neocortex evokes a stereotyped sequence of intracellular and extracellular potentials. In both cats [1, 2, 14] and monkeys [15] cortical stimulation evokes a striatal field potential characterized by an initial positive wave followed by a longer lasting negative wave, sometimes followed by a late rebound positivity. It has been suggested that the initial positive-negative wave sequence corresponds to the characteristic intracellularly recorded EPSP-IPSP sequence seen following cortical stimulation [2]. If so, the evoked potential could provide a complementary tool for assessing corticostriate relations, one that is especially amenable to pharmacological analysis.

In this report we examine the characteristics of the neostriatal evoked response that follows electrical stimulation of frontal cortex in rats and the correlations between field potential waves, extracellularly recorded action potentials and intracellularly recorded PSPs. The effects of kainic acid lesions of the medial thalamus on the evoked response are also described.

METHOD

Adult male Sprague-Dawley rats weighing 200–400 g were anesthetized with 1.25 g/kg urethane, IP, and installed into a stereotaxic apparatus with blunt earbars. Lidocaine ointment (5%) was applied to the ear bars and wound margins. Parallel, bipolar 200 μm formvar coated, stainless steel stimulating electrodes, cut bluntly, were implanted into the frontal cortex white matter (forceps minor of the corpus callosum) at coordinates A: 3.5 mm to bregma, L: 2.0, D: 2.0 mm below the cortical surface at a 20 degree angle anterior to the coronal plane [18]. Gray matter was stimulated at two sites in some animals: pre-limbic cortex (medial prefrontal cortex, cingulate area 3 according to Zilles [26]) at A: 3.2, L: 0.5, D: −2.0 and primary motor cortex at A: 3.0, L: 3.2, D: −1.5 [26]. Extracellular recording of single units and field potentials were made with 4–8 mohm glass pipettes filled with 2 M NaCl. Intracellular recording were made with 25–50 mohm glass micropipettes (2 mm, WPI Kwik-fil capillary tubing) filled with 2 M potassium methyl sulfate. Recordings with glass pipettes and wires were generally made near coordinates A: 0.0, L: 3.2–4.0, D: −3.5–−6.0. Field potentials were generally recorded with single 125 μ or 75 μ stainless steel wire electrodes. During intracellular recordings, a

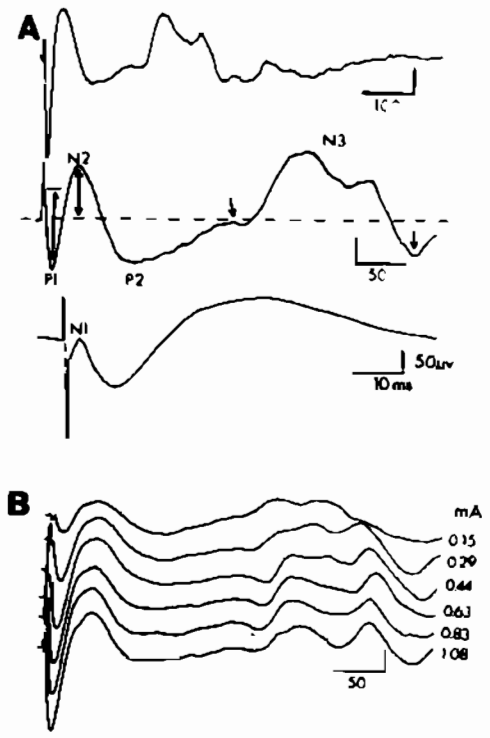

FIG. 1. A: Frontal cortex white matter stimulation evokes a stereotyped sequence of waves identified by their polarity (P or N) and order number. Typical responses from three different animals are shown at three time scales. Positivity is down in all figures for all extracellular traces. Evoked responses shown are averages of 12 consecutive responses. The measurement of P1 and N2 amplitudes is represented by the doubleheaded arrows. Wave N3 is often preceded and followed by small positive waves (small arrows). B: Increasing stimulus current causes a nearly linear increase in P1 amplitude. N2 increases amplitude and peak latency. Waves P2 and N3 are relatively unresponsive except at the lowest currents.

TABLE 1

LATENCIES OF COMPONENTS OF THE FRONTAL CORTEX WHITE MATTER STIMULATION EVOKED RESPONSES IN NEOSTRIATUM

Group	n	N1	P1 Peak	N2 Onset	N2 Peak	N2 End	N3 Onset
Intact	71	3.9 msec*	10.8	21.4	38.0	65.9	176.1
		0.08	0.1	0.3	0.6	1.0	1.8
Medial							
Thalamic	9†	4.4†	14.2‡	26.4‡	45.7†	81.2‡	—
Lesioned		0.4	0.7	1.1	1.9	3.5	—
Intact:	9						
Ipsilateral		4.0	10.8	21.5	39.5	71.3	190.0
		0.3	0.3	0.7	1.2	3.5	5.1
Contra-		4.5	12.5§	23.3§	42.0	68.7	193.3
lateral		0.2	0.7	0.8	1.5	2.3	5.9

*Mean (first line) and SEM (second line) shown.
†Six animals, 9 sides.
‡Different from intact, $p<0.001$.
§Different from ipsilateral side, $p<0.05$.

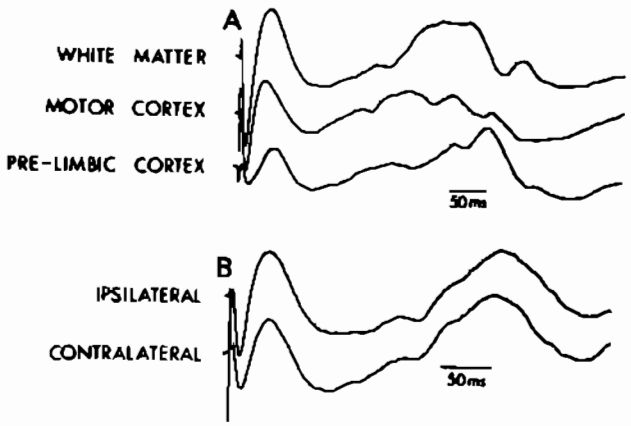

FIG. 2. A: Evoked responses recorded in the same animal at the same neostriatal site show the same sequence of waves following stimulation of white matter, motor cortex and pre-limbic cortex. White matter induces a response at the shortest latency, motor cortex at a slightly longer latency and pre-limbic cortex at the longest latency. B: Waves P1 and N2 are smaller and occur at a longer latency in contralateral as compared to ipsilateral neostriatum following white matter stimulation. In contrast, waves P2 and N3 are nearly indistinguishable on the two sides.

single wire electrode for recording field potentials was fixed at A: 0.0, L: 2.8, D: −5.0.

Cortex was stimulated with 0.1–0.2 msec, 0.1–2.0 mA square pulses at 0.2–0.8 Hz. Recording began at least 60 minutes after the electrode implantation.

Evoked potentials were recorded monopolarly with a Grass P15 amplifier referred to a wound margin ground and were collected on-line using a Marinchip M9900 computer and a 12 bit A/D converter at rates between 800 and 10,000 Hz. Half-amplitude frequency cutoffs of 1 and 3000 or 10,000 Hz were used. Averages of 12 consecutive trials were constructed on-line and stored on disk for subsequent analysis. During intracellular experiments, intracellular events and field potentials were digitized by a 12 bit Nicolet digital oscilloscope and stored on disc with a PDP 11-03 computer for subsequent analysis.

Chronically lesioned animals were anesthetized with 50 mg/kg sodium pentobarbital, IP, plus 1.0 mg/kg atropine methyl nitrate. Infusions of 0.5 μl of 1.25 μg/μl kainic acid solution were made through a 27 ga cannula. In 3 animals bilateral lesions were made in the medial thalamus at coordinates A: −3.0, L: 0.7 and D: −5.5. In three other animals, four infusions were made, two at the above coordinates and bilaterally at A: −4.0, L: 1.0 and D: −5.8. All lesioned animals survived 2–4 days prior to testing. Each animal received 60,000 units, IM, penicillin daily. Lesions, recording and stimulating sites were verified histologically, in tissue stained with neutral red.

In all figures, an upward deflection reflects a negative variation for evoked responses and depolarization for intracellular traces. P1 amplitude was measured as the difference between N1 and P1 peaks. N2 amplitude was measured as the difference between pre-stimulus baseline and N3 peak.

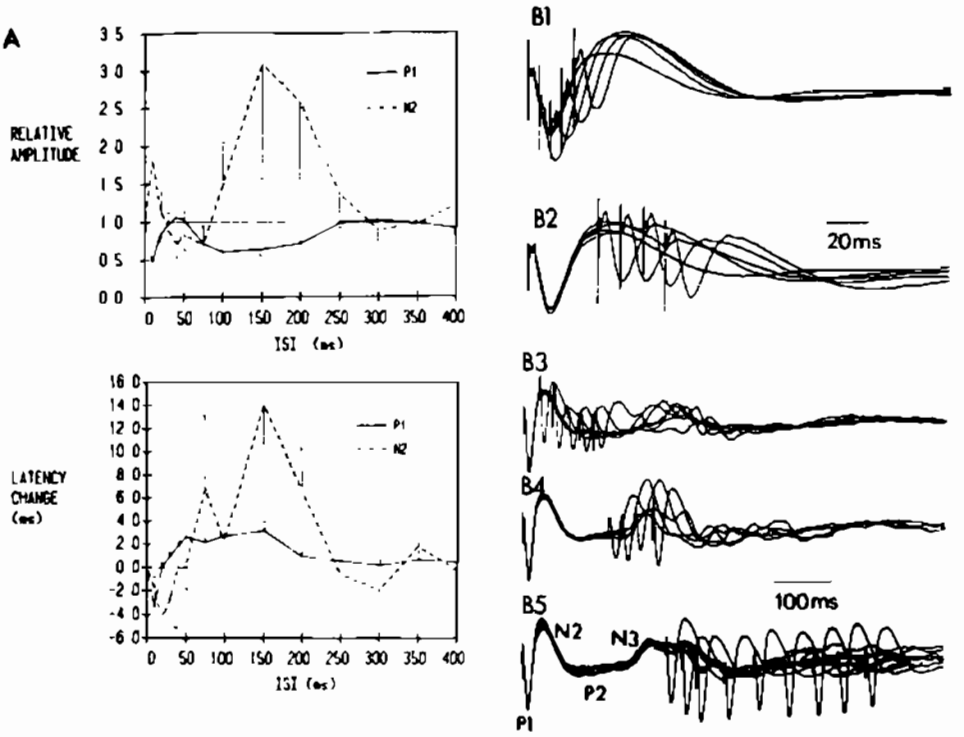

FIG. 3. A: Plots of the mean (N=4 animals) relative amplitude and change in latency of waves P1 and N2 to a test white matter stimulus at various interstimulus intervals (ISI) after an equal amplitude conditioning stimulus. SEM bars shown. B1–B5: Overlaid traces of conditioning and test responses at various interstimulus intervals.

RESULTS

Characteristics of Evoked Potentials

Electrical stimulation of frontal cortex white matter evoked a stereotyped sequence of potentials (Fig. 1A). A very small initial negative response (N1, see latencies in Table 1) was rapidly followed by a large, positive wave (P1) of 14–16 msec duration. This was succeeded by a flatter, approximately 45 msec duration negative wave (N2). An inflection was often seen on the rising edge of N2 (see Fig. 5B) and occasionally on the downward edge of N2. N2 was followed by a shallow, broad positivity of 80–130 msec duration. A late, complex negativity (N3), which was often preceded by a plateau or small positivity (Fig. 1, arrow) usually followed P2. N3 was most commonly composed of two successive negative humps, though in some cases either a single wave or three or more waves were evident. In many cases a small negative wave followed N3. The precise form of N3 often varied gradually during the experiment and was very susceptible to drug treatment (unpublished observations).

P1 amplitude increased with increased stimulating current over much of the tested range (Fig. 1B). P1 peak latency was unchanged, except in several animals where the latency decreased approximately 0.5 msec at the highest currents. In contrast, N2 amplitude increased over the lower half of the current range and then stabilized; peak latency increased over the entire current range. The latency to N3 increased slightly with increasing current, whereas N3 amplitude was relatively independent of current intensity, except that at the lowest currents both amplitude and latency sharply declined (Fig. 1B).

Comparison of Neostriatal Evoked Potentials Following Stimulation of Various Cortical Regions

Evoked potentials with nearly identical characteristics could be recorded throughout most of the head of the neostriatum when frontal cortex white matter was stimulated. The largest amplitudes of P1, N2 and N3 were typically found in dorsal and central neostriatum (Fig. 6).

A similar evoked potential was recorded in the contralateral striatum. P1 was slightly smaller in amplitude and approximately 1.7 msec longer latency than in the ipsilateral neostriatum (Fig. 2B and Table 1). N3 occurred at the same latency on both sides.

Stimulation of gray matter in motor cortex or pre-limbic cortex evoked field potentials of lower amplitude and longer latency, for the same stimulating current, than was seen after white matter stimulation (Fig. 2A). The peak of P1 following pre-limbic cortex stimulation was typically reached 3 msec or more later than after white matter stimulation.

Paired Conditioning-Test Cortical Stimulation

With paired equal magnitude conditioning and test stimuli delivered to frontal cortex white matter, the amplitude and latency of test P1 and N2 varied systematically with the interstimulus interval (Fig. 3). The most notable features are best described relative to the individual components evoked by the conditioning stimulus. During conditioning wave N2, the test P1 amplitude was unchanged; P1 amplitude began to decline on the falling phase of N2 (Fig. 3B2, 3B3). Test N2 amplitude is reduced and its duration shortened during the peak and falling phase of N2 (Fig. 3B1). In contrast, during

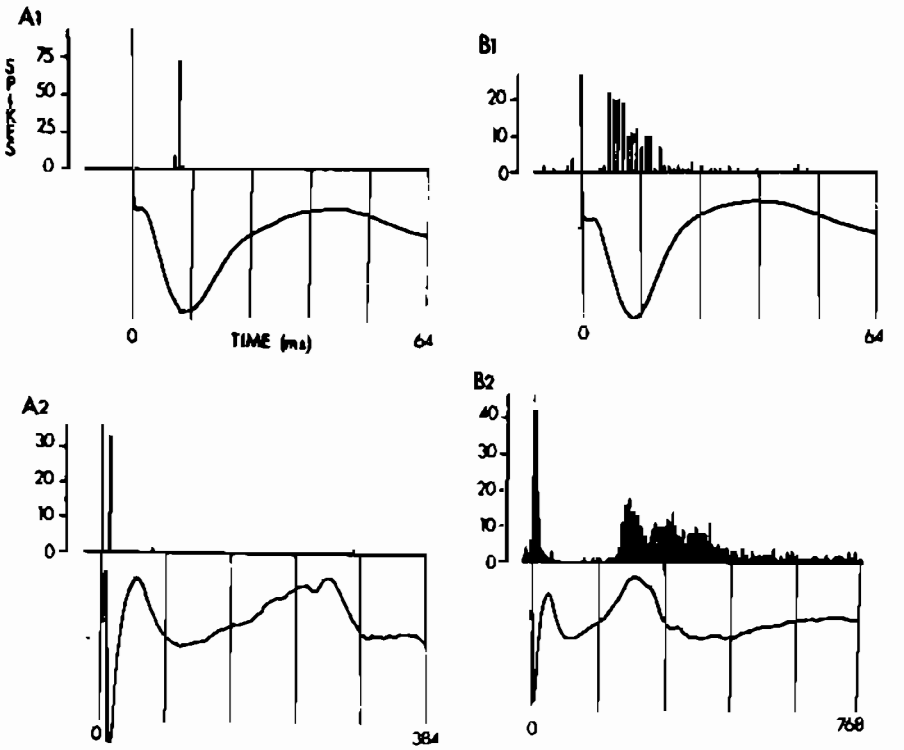

FIG. 4. Comparison of single unit peristimulus time histograms with the simultaneous average evoked potential recorded from the same microelectrode. Notice the small notching, especially prominent in A1, signifying the contribution of action potentials to the evoked response. A1, A2: Two nearly silent neurons activated during P1; shown at two time scales. B1, B2: Two spontaneously active neurons. Both cells show an increased probability of firing during P1 and an inhibition of firing beginning during wave N2. When shown at a longer time scale (B2) the inhibition of firing during P2 and the rebound excitation during N3 are obvious. In all cases the greatest firing is seen during the steepest slope of wave P1. Notice that wave N1 precedes the onset of stimulus-induced firing.

conditioning P2, P1 amplitude is reduced and peak latency is increased. N2 amplitude is reduced, but its duration returns nearly to normal (Fig. 3B2, 3B3). During conditioning wave N3, test P1 amplitude and latency recover and test N2 amplitude, peak latency and duration greatly increase (Fig. 3B5). Both test P1 and N2 return to normal values after N3.

Correspondence Between Field Potential Waves and Extracellular Unit Activity

Extracellular unit activity (n=23) was most commonly evoked during waves P1 and N3. Silent neurons were typically activated only during P1 (Fig. 4A), though in some cases during both P1 and N3, and rarely only during N3. Spontaneously active neurons showed an increased probability of firing during P1 and N3 and a distinct, nearly complete depression during N2 and continuing throughout P2 (Fig. 4B).

Correspondence Between Field Potential Waves and Intracellular Activity

Field potential fluctuations correlated with intracellularly recorded potentials (Fig. 5). N1 preceded the onset of any intracellular activity. In most neurons the peak of the stimulation evoked EPSP (mean=12.0 msec, SEM=0.40, n=26) coincided with the peak of P1 (mean=11.3, SEM=0.25; difference: $t(25)=-1.78$, ns). The amplitude and latency of the EPSP and P1 varied in parallel over a range of stimulating currents (Fig. 5C). In three cells (of 26) the EPSP had a much slower rise and reached peak 3.3 to 7.6 msec after the peak of P1.

N2 was related to intracellular events in a more complex manner. The rising phase of N2 corresponded to the falling edge of the initial EPSP. An inflection seen in the rising phase of N2 was typically coincident with a sharp reduction in the slope of the falling phase of the initial EPSP (Fig. 5B). The peak of N2 and its falling edge occur as the hyperpolarization deepens.

P2 corresponds to the flat, prolonged portion of the hyperpolarization. The latencies to the onsets of the rebound depolarizations were variable across cells, but were centered around the plateau and small positive deflections that define the onset of N3. N3 itself was coincident with the rebound depolarization, though no clear correspondence between specific waves within the N3 complex and intracellular events were noted.

Effect of Kainic Acid Lesion of the Medial Thalamus

Bilateral injections of kainic acid at one medial thalamic site were made in 3 rats and at two sites in 3 other rats. In

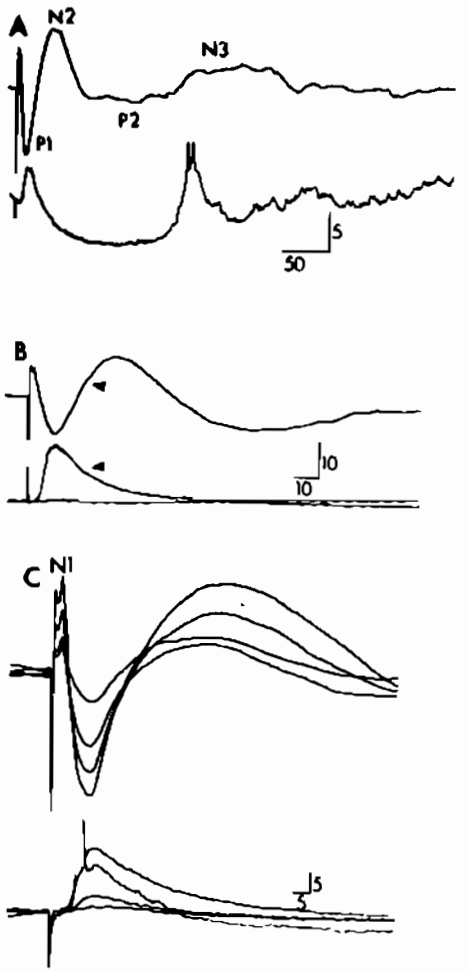

FIG. 5. Comparison of intracellular events with extracellularly recorded evoked potentials. A: In a typical neuron, the initial EPSP (lower curve) corresponds closely with wave P1 (upper curve). During the intracellularly observed hyperpolarization, two extracellularly recorded waves occur—N2, which begins during the falling phase of the EPSP, and P2, which corresponds to the last 2/3 sec of the hyperpolarization. Wave N3 begins at approximately the beginning of the rebound depolarization that succeeds the hyperpolarization. B: The correspondence between P1 and N2 with the EPSP and the beginning of the hyperpolarization is shown at a faster sweep for another cell, from another animal. The intracellular record is superimposed on an extracellular control recorded immediately after leaving the cell. Note the close temporal correspondence between an inflection (arrow) of the rising limb of N2 and an inflection of the falling edge of the EPSP. C: Evoked potential wave P1 responds similarly to the EPSP to changes in stimulus current (0.3, 0.6, 1.0, 1.6 mA shown). Note that wave N1 precedes the onset of the EPSP. All traces are averages of 6 consecutive responses. Action potentials are truncated in A and C. Calibration bars signify millivolts for intracellular traces and milliseconds for all traces.

one-site rats, damage was seen throughout most of the medial thalamus and much of the anterior thalamus, in once case extending into the septum. Lateral thalamus, the posterior nuclei, lateral geniculate and reticular nucleus were undamaged. The medial and lateral habenula and paraventricular nucleus, though situated amidst extensive degeneration, remained intact. In all 3 rats the parafasciculus/centromedian was intact. In these rats, evoked potentials with all of the standard waves present were recordable throughout much of the neostriatum following white matter stimulation, though, in some regions, N3 was absent. In these rats, as well as those with more complete lesions (below), the latencies to waves P1 and N2 were lengthened (Table 1).

In the 3 rats that received bilateral injections at two different medial thalamic sites, much of the lateral thalamus and the reticular nucleus remained intact. The lesions, though, extended posteriorly to include the parafasciulus nucleus, the pretectal area and portions of the deep layers of the superior colliculus. The majority of thalamic sources of neostriatal afferents were destroyed. In these cases, N3 was nearly or completely absent throughout the head of the neostriatum. Figure 6 compares the depth distribution of the evoked response from the overlying neocortex (primary somatosensory cortex [26]) at bregma down to the ventral striatum for an intact and 2-site medial thalamic lesioned rat. Notice that in the intact animal temporally coincident late waves are present in both the neocortex and the neostriatum, whereas in the lesioned animal late waves are present only in the cortex. In this animal, both the ventroposterior lateral nucleus and the reticular nucleus are intact, providing a possible thalamic substrate for modulating the late cortical waves, but the vast majority of the thalamic innervation of the neostriatum was destroyed.

DISCUSSION

The potentials evoked in rat neostriatum by stimulation of the cortex are similar, in many respects, to those previously reported to occur in cats [1, 2, 14] and monkey [15]. A similar response, though differing in the precise latencies and amplitudes of the individual waves, can be evoked from frontal cortical white matter and from distinct cortical areas known to project into the neostriatum. And, following white matter stimulation, similar evoked responses could be recorded in ipsilateral and contralateral neostriatum.

Interpretation of Specific Evoked Potential Waves

The neostriatum is an unlayered telencephalic mass lying beneath the cerebral cortex. In the rat it is perforated by fascicles of the dispersed internal capsule. The vast majority of cells, comprising perhaps 90% or more of all neostriatal neurons, are medium diameter (12–20 μ) cells with 4–6 spine infested dendrites [17]. Typically the dendrites are radially oriented, except along the margins separating striasomes and matrix where the dendritic fields are flattened or otherwise distorted [23]. This internal structure makes interpretation of current flows, and hence extracellular potentials, difficult. One striking example of this complexity is that two waves, P1 and N3, of opposite polarity, were clearly coincident with cellular depolarizations and spike initiation. However, notwithstanding these complications, we have determined several reliable correlations between intracellular events and extracellular potentials.

Wave N1. Since N1 is small and precedes the onset of the intracellularly recorded EPSPs and extracellularly recorded evoked neuronal spiking, it probably represents two related events: (1) the synchronous activation of terminals of the fastest corticostriatal projection neurons and (2) the synchronous passage of action potentials in rapidly conducting cortical projection neurons that traverse the neostriatum in the fascicles of the internal capsule. A negative wave corre-

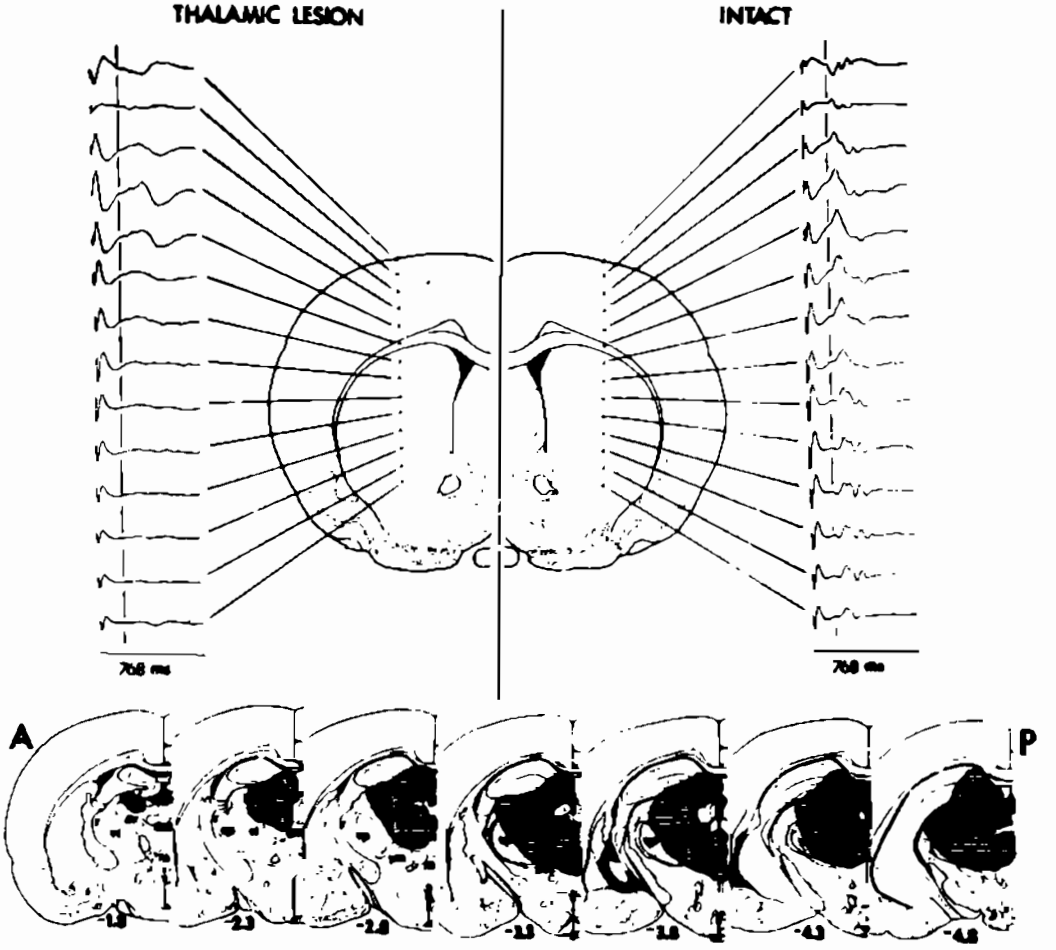

FIG. 6. Medial thalamic lesions made with kainic acid eliminate the late negative wave (N3) within the neostriatum, but not the equivalent wave seen in the overlying somatosensory cortex. Depth series of responses from the surface to −6.50 mm at 0.5 mm steps are shown for an intact and for a medial thalamic lesioned rat. A vertical line is drawn near the onset of wave N3 for both sets of traces. The thalamic lesion is outlined in the seven section shown (after Paxinos and Watson, 1982). The lesion continued posteriorly for 1–1.5 mm and damaged portions of the superior colliculus and the pre-tectal area (not shown). Thalamic lesion also increased the latency to waves P1 and N2.

sponding to more slowly conducting fibers is probably obscured by P1.

Wave P1. All previous reports of cortical stimulation evoked neostriatal potentials have described an initial positive wave [1, 2, 14, 15]. This wave, P1, probably represents the mean extracellular field produced by the synchronous depolarization of a large number of neostriatal neurons. In our experiments, P1 corresponds closely to the intracellularly recorded EPSP, the peaks coinciding within 1.5 msec for 23 of 26 neurons. Furthermore, EPSP amplitude and P1 amplitude covaried over a range of stimulating currents. And, in accord with reported corticostriatal projection latencies [23], P1 in the contralateral neostriatum reached peak later than in the ipsilateral neostriatum.

Unit firing is most pronounced during the initial rise of P1, reminiscent of observations that unit activity occurs during the steepest slope of evoked responses recorded elsewhere (e.g., [22]).

It is interesting that 3 of the 26 neurons showed a slower rise and later peak of the initial EPSP to white matter stimulation. Since P1 following pre-limbic cortex stimulation has a slower rise and a later peak than P1 following motor cortex stimulation, the long latency cells might be preferentially innervated from cortical regions, such as pre-limbic cortex, which have slower projections. Such segregation of cortical input has recently been demonstrated in the rat [5].

Waves N2 and P2. The rising edge of N2 correlates with the decline of the initial EPSP. The inflection often seen on this limb corresponds with a sudden decrease in the slope of the falling edge of the EPSP, suggesting the end or the onset of an active process.

The observed intracellular hyperpolarization corresponds to two extracellularly recorded waves. N2 overlaps the onset and first portion of the hyperpolarization and P2 overlaps the remainder of the hyperpolarization suggesting that two separate processes may contribute to the hyperpolarization. Hull and coworkers [7] first hypothesized a bipartite hyperpolarization on the basis that the negative-going portion of the hyperpolarization had different properties than did the period after peak negativity was reached. Based upon N2's latency (immediately following P1) and duration (about 40 msec), we speculate that N2 may be the extracellular correlate of intrastriate collateral inhibition [10, 12, 16]. P2, in contrast, may correspond to the disfacilitation (decline in

tonic excitatory input) identified by Wilson and colleagues [24] that accounts for most of the hyperpolarization.

The paired conditioning-test stimulation experiments also suggest two processes. When the test pulse EPSP correlate (wave P1) occurred during conditioning pulse evoked wave N2, P1 amplitude was unaffected. In intracellular conditioning-test cortical stimulation experiments, test EPSPs reach the same absolute amplitude as conditioning EPSPs during this phase [7,21]. Consistent with the idea that N2 is the correlate of intrastriate collateral inhibition is the finding that cortex stimulation-induced EPSP amplitude is not reduced by collateral inhibition [16]. In contrast, when the test P1 overlaps the conditioning pulse-induced P2, P1 amplitude is reduced. In intracellular studies, test EPSP amplitude does not reach the absolute membrane potential reached by the conditioning EPSP, however it does achieve the same relative amplitude from the hyperpolarized membrane potential as the conditioning EPSP reaches above resting membrane potential [7,24].

N2 and P2 also respond differently to changing stimulus intensities. N2 increases in amplitude and shifts peak latency with increasing stimulus current whereas P2 is less responsive to changes in stimulus current.

We also observed a systematic increase in latency to the peak of test P1 beginning during N2 and reaching and remaining at the maximum latency shift during P2. A similar latency shift to the peak of test EPSPs during this phase, though not previously discussed, can be measured in previously published figures (e.g., [7], Figs. 1 and 2; [24], Fig. 1F).

Wave N3. The onset of N3 roughly corresponds to the rising edge of the depolarization that succeeds the hyperpolarization. N3 corresponds to an intracellularly observed complex EPSP and an increased likelihood of cell firing. Unlike the late rebound wave observed in cat [2,14], the polarity of this wave is opposite of the extracellular potential corresponding to the initial EPSP. We might speculate that this suggests the pattern of afferent activation causing the initial and rebound somatic depolarizations are sufficiently different that they induce reversed extracellular current flows in the rat.

Role of the Medial Thalamus in Modulating Cortical Evoked Neostriatal Potentials

In all animals with medial thalamic lesions, we observed an increase in the latency to all of the evoked waves that were present. Although thalamic afferents probably contribute directly to portions of the neostriatal evoked potential, the medial thalamic lesions could also alter neostriatal response to cortical stimulation in a more indirect manner. In twin pulse experiments, the latency to P1 was increased when P1 was initiated during the presumed disfacilitation phase of the hyperpolarization (during wave P2). It is possible that medial thalamic lesions reduce the tonic afferent depolarization of neostriatal neurons and this loss is responsible for the latency shift of the cortical evoked potential.

The medial thalamus is of importance in the genesis of the late rebound depolarization represented by wave N3. A midline structure like the medial thalamus might be required to account for the synchronization of N3 onset in the ipsilateral and contralateral neostriata. We have confirmed the suggestion [14] that the late wave requires an intact medial thalamus to occur. In animals with kainic acid lesions, which avoid the interpretational problems Liles [14] raised for his acute electrolytic lesions, the parafasiculus/centromedian appeared to be of particular importance for the expression of wave N3. Smaller kainic acid lesions, which damaged much of the midline and intralaminar thalamus but spared the parafasiculus/centromedian, did not eliminate N3.

It is also of some interest that the late wave observed in the overlying sensorimotor cortex is not disrupted by large medial thalamic lesions. In all cases, this cortical area's primary thalamic projection nuclei, VPL and VPM, remained intact, as did the thalamic reticular nucleus. Hence we may conclude that the midline thalamus is not essential for the late wave to be expressed in the neocortex, but is essential for the late wave in the neostriatum.

Conclusion. Although the neostriatum is an unlayered structure with a complex internal organization, a close correspondence exists between the extracellularly recorded evoked potential and cellular events. This probably reflects the synchronous activation of a similar sequence of PSPs in large numbers of neostriatal neurons. We believe the identification of these correspondences is essential if neostriatal evoked potentials are to be used successfully as a tool for studying corticostriatal relations.

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