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EFFECT OF 2-AMINO-5-PHOSPHOPENTANOIC ACID (AP5), A GLUTAMATE NMDA RECEPTOR BLOCKER, ON NEURON ACTIVITY IN THE CAT MOTOR CORTEX DURING PERFORMANCE OF A PAW PLACEMENT CONDITIONED REFLEX

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Two types of stimulus-associated response were recorded in the contralateral motor cortex during performance of a condition reflex consisting of placing the forepaw on a support in response to a short electrical stimulus (4 msec, 500 Hz) applied to the contralateral parietal cortex (field 5). Primary short-latency responses (peak latent period about 10 msec, duration 30-50 msec) showed little sensitivity to the application of AP5, a blocker of glutamate NMDA receptors; secondary long-latency responses (peak latent period 65 msec, duration 150-200 msec) were inhibited in 44% of cases. Excitatory neuron responses associated with movement were inhibited by AP5 in 18% of cases. Increases in the latent period of the movement itself were seen in 19% of cases. AP5 decreased background activity in 46% of background-active neurons. The number of cases in which individual components of the response and neuron background activity were increased and latent periods of movement were decreased after application of AP5 was no more than expected from a random spread of data.

Positive reinforcement of movements elicited by relatively prolonged (300-500 msec) electrical stimulation of the parietal cortex results in conditioning in that the animal learns to produce the movement voluntarily [26] and in response to short (2-4 msec) stimulation of the cortex, which prior to training produced only slight shuddering of the paws [8].

Analysis of neuron activity in the motor cortex has demonstrated that during the performance of conditioned reflex movements developed in response to short stimulation of the parietal cortex, a repeated spike of excitation is generated in the inhibitory pause following the primary excitatory response in untrained animals, and this is followed by a third, movement-associated phase of the response [8]. It was suggested that generation of the secondary excitation in response to the conditioned signal is based on activation of ion channels controlled by glutamate receptors of the NMDA type [5]. Activation of glutamate NMDA receptors underlies the generation of motor commands in the spinal column [16] and launches processes which alter the efficiency of synaptic transmission in the neocortex and hippocampus [13, 19]. It was of interest to study the functional role of NMDA-type receptors in the motor cortex, where these functions could be used during the development and performance of a conditioned movement reflex.

METHODS

Studies were carried out on adult cats with a previously developed conditioned reflex consisting of placing the paw on a support in response to a short-duration electrical stimuli (2-4 msec, 500 Hz, 0.2 msec) applied to the parietal cortex (field 5, AP = 13-15, L = 7.5), stimulation of which prior to training using long-lasting (300-500 msec) series of impulses pro-

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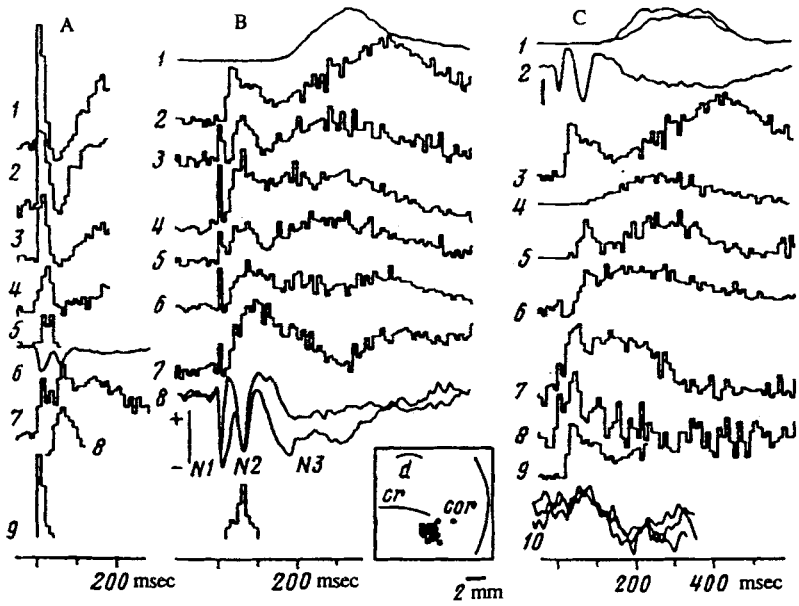

Fig. 1. Component composition of cat motor cortex neuron responses to stimulation of the parietal cortex. Horizontal axes show time, msec; PSH show the mean numbers of spikes per 10 msec; histograms of latent period distribution (*A*, 9; *B*, 9) show the numbers of responses to latent periods within the specified interval; the insert below shows the recording region in the projection on the surface of the pericruciate cortex (d = dimle; cr = s. cruciatus; cor = s. coronalis); each point corresponds to several placings of the microelectrode. *A*) Reaction component *I*. *1-5*) Component *I* of the responses of a single neuron to stimulation of the parietal cortex at different stimulation strengths (8, 6.5, 5, 3, and 2 V respectively); *6*, *7*) focal potential (*6* shows negativity downgoing), recorded simultaneously with the responses of another neuron (*7*); *8*) fragment of reaction *1*, *B*, *3*; *9*) distribution of latent periods for maxima of response component *I* ($t \pm \sigma$ = 10 ± 7 msec, n = 38). *B*) Reaction component *II*. *1*) Averaged trajectory of paw movement; deviations upward correspond to paw elevation; *2-7*) variants of response component *II*; *8*) focal evoked potentials recorded in two animals. Calibration: 250 μV, negativity downgoing; each curve is the average of 50 performances; *9*) distribution of latent periods for maxima of reaction component *II* ($t \pm \sigma$ = 65 ± 18 msec, n = 48). *C*) Reaction component *III*. *1*) Averaged trajectory of paw movements in two experiments on different animals; *2*) averaged focal evoked potential. Calibration: 250 μV, negativity downgoing, n = 50; *3-7*) examples of the dynamics of reaction component *III* during the placing of the paw on the support; *8*) averaged response of the same neuron as in Fig. 1, *C*, *7* during episodic nonelevation of the paw; *9*) fragment of the reaction shown in Fig. 1, *B*, *2*; *10*) focal potentials during movement delay; the end of each trajectory corresponds to the start of paw elevation.

duced coordinated movements of the contralateral forepaw resembling the placing reflex [4]. During experiments, cats were gently immobilized in a sling to limit movement. A horizontal screen at chest level prevented the animal from seeing its forepaws. Conditioned signals were presented at intervals of 5-15 sec.

Neuron activity and focal potentials were recorded using three-channel glass micropipettes after initial removal of the dura mater from the area of the motor cortex, whose neurons were intensely activated during voluntary elevation of the paw (Field 4γ, Fig. 1). The recording channel of the micropipette was filled with 1 M NaCl (resistance 3-6 MΩ at 1 kHz), and the other two channels were filled with 100 mM D,L-AP5 (pH 8-9, phoresis current 10-70 nA, constant cut-off current 5-10 nA) and 165 mM isotonic NaCl (compensatory current equal in amplitude and of opposite sign to the phoresis current). A two-

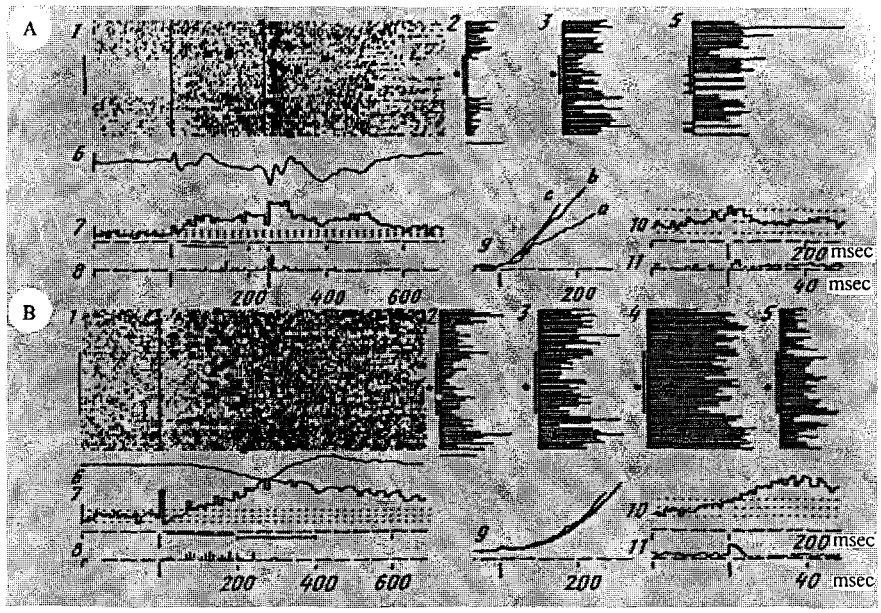

Fig. 2. Effects of microapplication of AP5 on motor cortex neuron responses and movements. *1*) Scan representations of neuron activity: each row corresponds to a sequential (from above downwards) test of the conditioned reflex; points correspond to neuron discharges, and squares to movement onset; vertical lines show the moment at which the parietal cortex was stimulated with two impulse trains, of which only the first is usually used; *2-4*) histograms showing the mean frequencies of background (*2*) and evoked (*3*, *4*) activity during sequential trials of the conditioned reflex; each horizontal segment corresponds in fragment *2* to the mean frequency of background activity in the neighboring row of the scan and in fragments *3* and *4* to the mean frequency of evoked activity in the neighboring rows of the scan, indicated on fragment *7* with continuous horizontal lines beneath the abscissa. Calibration: 100 spikes/sec; *5*) histogram of latent periods of movements in sequential trials. Vertical lines on fragments *2-5* show the time of AP5 application; asterisks show statistically significant ($p \leq 0.05$) deviations; *6A*) focal evoked potentials averaged for all trials. Calibration: 250 μV, negativity downgoing; *6B*) paw movement trajectory averaged for all trials. Deviations downward correspond to elevation of the paw; *7*, *11*) averaged neuron response PSH. The abscissa shows time after the end of parietal cortex stimulation, msec; the bin widths were 10 msec (*7*) and 2 msec (*11*); the ordinate shows the instantaneous spike frequency averaged for all rows of the scan in the interval corresponding to one bin. Calibration: 50 spikes/sec (*A*), 100 spikes/sec (*B*); *8*) histogram showing the distribution of latent periods of movement. The abscissa shows latent period duration, msec, and the ordinate shows the numbers of responses with specified latent periods; *9*) cumulative PSH; the abscissa shows time (msec) after stimulation of the parietal cortex and the ordinate shows the total deviation of the mean instantaneous frequency of evoked activity accumulated to this time, as a proportion of the mean background activity level; *a*) before, *b*) during, and *c*) after application of AP5; *10*) histograms showing the mean instantaneous frequency of discharges averaged relative to movement onset with a 10-msec step; dotted lines on the time histograms (*7*, *10*, *11*) show values of $\bar{f}$, $\bar{f} \pm 2\sigma$, where $\bar{f}$, σ are the mean and standard deviation of the mean of the instantaneous background activity frequency.

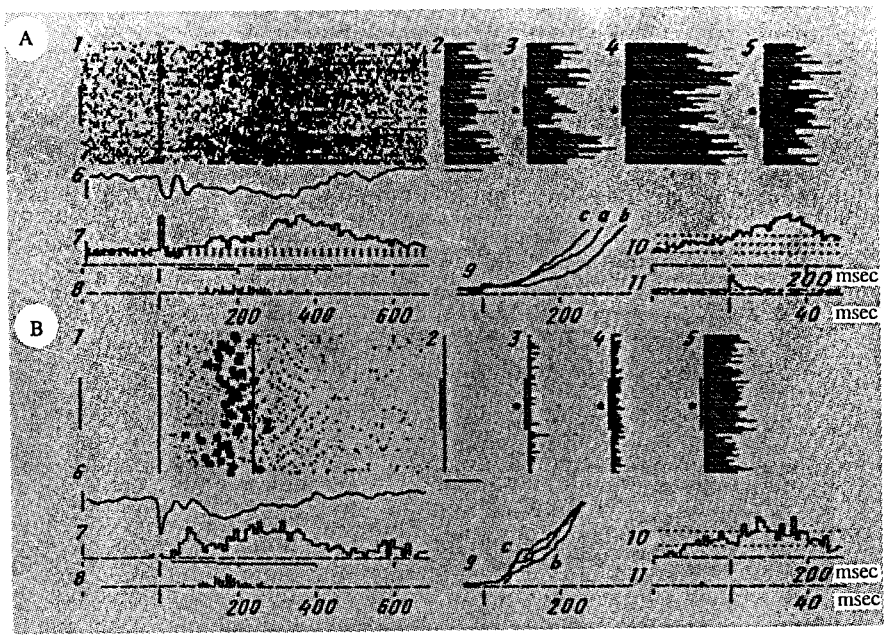

Fig. 3. Effects of microapplication of AP5 on motor cortex neuron responses and movements. For further details see caption to Fig. 2*A*. Calibration: *A*) 125 μV, 100 spikes/sec; *B*) 125 μV, 10 spikes/sec.

channel electronic stabilizer was used to maintain a constant phoresis current in the range −250 to +250 nA independently of micropipette resistance.

A microelectrode was implanted using a mechanical manipulator attached to a animal's head, allowing placement on the cortical surface with an accuracy of 0.2 mm. Spikes from individual neurons and groups of identically responding cells were isolated an amplitude-time discriminator [2] and were entered into a computer via an interface for subsequent processing.

Movements were recorded from the forelimb by attaching a small lamp, which illuminated light-sensitive elements fixed to the lower surface of the screen. Movement onset was detected by passing the amplified light detector signal through a discriminating condenser to a threshold detector whose input was transiently grounded at the moment the conditioned signal was switched on, using a computer-controlled electronic switch. Thus, paw position in the post-stimulus period was always determined from a null level which was independent of its previous position. The point of movement onset was taken as the moment at which displacement of the paw position from the null level reached a threshold value which was determined experimentally with the condition that the duration of the deviation was greater than some empirically selected value (usually about 200 msec).

Responses limited by time interval T were analyzed statistically in terms of mean discharge frequencies during time T in sequential tests (n) of the conditioned reflex, given by $\{f_n^T\} = \{f_1^T, f_2^T, \ldots\}$, where $f_n^T = x_n^T/T$ and x_n^T is the number of spikes in time T in test n, which were compared pairwise with corresponding background activity values using the Wilcoxon criterion with a "soft" level of significance ($p < 0.05$).

The action of AP5 was evaluated by taking a set of mean frequency values $\{f_n^T\}$ during continuous periods of exposure lasting 3-5 min and comparing this with sets of mean frequencies before and after exposure and, if the latter two groups were not significantly different from each other, with the combined control set. Application of AP5 was considered to affect neuron activity if the Wilcoxon–Mann–Whitney criterion calculated statistically reached the 5% level on comparison of the "effect" set with both of the control sets or with the combined control set.

This statistical criterion presupposes that the data are independent (sequential mean frequencies $\{f_n^T\}$). One reason for which this independence condition might be broken could consist of changes in the animal's state during sequential tests of the conditioned reflex. To remove any apparent linear trend from the $\{f_n\}$ data, values corresponding to the linear regression curve $\{\hat{f}_n\}$ were subtracted and comparisons were made between groups of corrected values $\{f_n^*\} = \{f_n - \hat{f}_n\}$ [1]. More com-

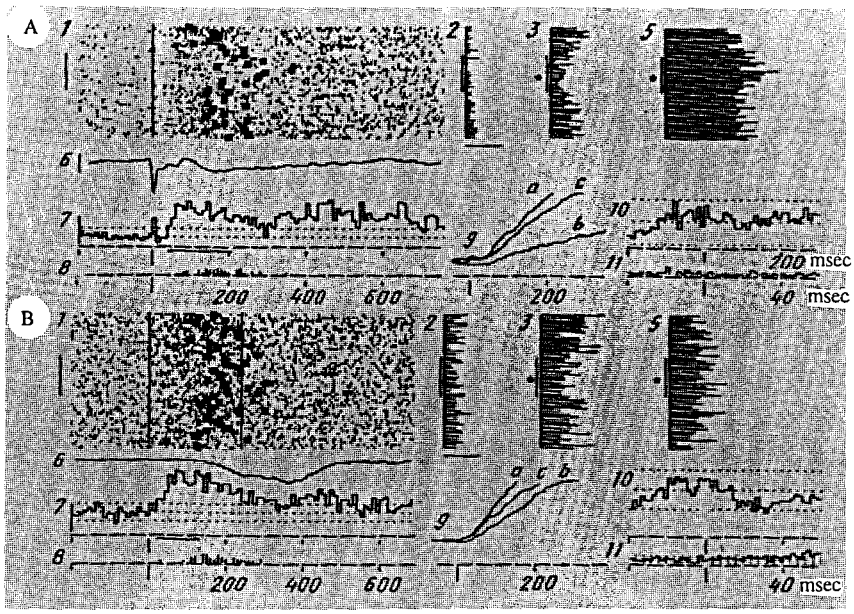

Fig. 4. Effects of microapplication of AP5 on motor cortex neuron responses and movements. For further details see caption to Fig. 2*A* and *B* respectively. Calibration: *A*) 250 μV, 50 spikes/sec; *B*) 50 spikes/sec.

plex trends and other possible sources of data dependence were not considered, with the result that there is a level of approximation in the assessments of the effect of AP5 in each individual experiment.

Considering those experiments in which changes in neuron activity due to application of AP5 satisfied the 5% significance level ($p \leq 0.05$) to be successful, it would be expected that an average of 5 of each 100 experiments would be "successful" without application of AP5 because of random variation of the data. For example, consider the situation in which the activity of 9 of 100 neurons changes significantly ($p \leq 0.05$) during application; is there a statistical basis for considering that the substance of interest has an effect on the activity of some neurons? This question can be addressed by assessing the binomial probability that 9 or more unlikely (here $p = 0.05$) events ("successes") would occur in 100 trials. Since the question is meaningful only in relation to rare events seen in a small proportion of tests, the desired probability can be evaluated using a Poisson approximation of the binomial distribution [3, 11]. The probability that k successes will occur in n experiments with a success probability of p is calculated from:

$$b(k; n, p) \approx ((np)^k/k!)e^{-np}.$$

The probability of successes in k or more experiments is:

$$p_k \approx 1 - \sum_{0}^{k-1} \frac{(np)^k}{k!} e^{(-np)}.$$

For example, the probability that rare ($p = 0.05$) "successes" will occur 9 or more times in 100 experiments, $p_9 \approx 0.068 > 0.05$.

RESULTS

Figure 1 shows examples of neuron responses and focal evoked potentials (EP) recorded from the lower layers of the anterolateral part of the pericruciate cortex in well-trained animals systematically performing the conditioned reflex in response to short stimulation of the parietal cortex.

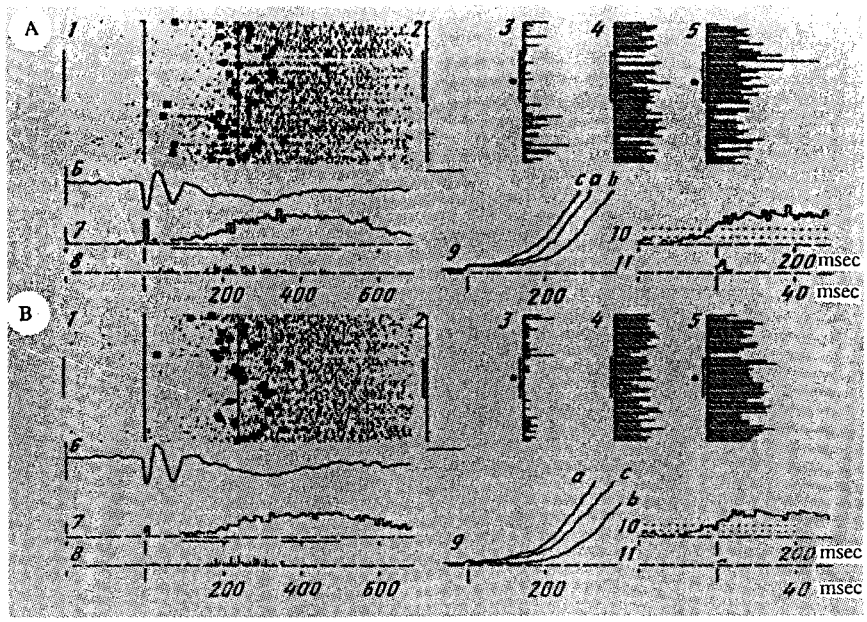

Fig. 5. Effects of microapplication of AP5 on motor cortex neuron responses and movements. For further details see caption to Fig. 2*A* and *B*. Calibration: 250 μV, 50 spikes/sec.

Three negative components can be seen in the focal EP: *N*1, *N*2, and *N*3 (Fig. 1*B*, *8*). With the time resolution used here (5 msec), the latent period of peak *N*1 was about 10 msec; the latent period for the start of the *N*2 wave was less than 30 msec, with a peak at about 70 msec; wave *N*3 started with a latent period of about 150 msec.

Comparison of Fig. 1*C*, *1* and Fig. 1*C*, *2* shows that component *N*3 developed in parallel with paw movement. The temporal coincidence of component *N*3 with the motor response cannot be explained as a recording artifact due to changes in the capacitative connection to earth of the high-resistance input of the amplifier occurring on mechanical displacement of the paw. Figure 1*C*, *10* shows a number of examples in which the potential underwent negative displacement long before the movements started (the end of the EP curve). Physiological rather than mechanical causes therefore underlie the generation of the *N*3 component.

Neuron responses to the conditioned signal also showed three components (different neurons showing these at different intensities and sometimes lacking components). The primary response (*I*) usually reached a peak 10 msec after stimulation ended, and lasted no more than 30-50 msec (Fig. 1*A*). As the stimulation strength decreased (from above downwards in Fig. 1*A*, *1-5*), the size of response *I* decreased and the time taken to reach the peak increased.

A second spike of neuron activity (*II*) was generated after the primary response or independently of it. Figure 1*B* shows different variants of response *II* — from relatively short-latency, fast-peaking responses (Fig. 1*B*, *2*) to responses which developed and decayed more slowly (Fig. 1*B*, *7*). The minimum latent period of component *II* was 20-30 msec (Fig. 1*B*, *2*, *4*); the mean time to its peak was 65 msec and coincided with the latency of the peak of component *N*2 of the EP (compare Fig. 1*B*, *9* and *B*, *8*); the maximum duration was 150-200 msec. Comparison of the dynamics of neuron activity with the paw movement trajectory (Fig. 1*B*, *1*) shows that component *II* reached a peak and could be essentially ended by the star of movement and its corresponding EP component *N*3.

Figure 1*C* shows examples of the third (*III*) component, directly associated with paw movement. The upper part of this figure shows examples of the movement trajectory and focal EP. The peak of component *III* is seen to coincide with or anticipate the maximum elevation of the paw, but usually occurred after movement started. The neuron responses shown in Fig. 1*C*, *7* were summed during performance, and those in Fig. 1*C*, *8* were summed during episodic non-performance of the conditioned reflex; in the latter case, the movement-associated response component disappeared, while the secondary response, associated with the signal, remained. For comparison, Fig. 1*C*, *9* repeats the example of response component *II* from fragment *B*, *2*.

Another example of the "dissection" of a complex peristimulus histogram (PSH) into individual components is shown in Fig. 1*A*, *5-8*: trace *A*, *5*, shows a standard for response *I*, consisting of an example of a response to a relatively weak (row *A*, *1-5*) stimulation of the parietal cortex; *A*, *8* shows a standard for response *II*, taken from fragment *B*, *3*. Comparison of the PSH in Fig. 1*A*, *7* with standards (*5* and *8*) and the focal potential recorded in parallel (*6*) allows three components to be identified.

Figures 2-5 show examples of the effect of AP5 on "background" and evoked neuron activity during performance of the conditioned reflex. Analysis of the component composition of responses allowed the effects of AP5 to be assessed separately for response *I*, evoked activity in the interval from 30-70 msec to 150-240 msec (allowing for the forms of particular PSH), which was usually occupied by component *II* of the response, and in the interval from 200-300 msec to 400-500 msec, around the peak of component *III*. Figure 2*A* shows an example of the completely reversible inhibition of background activity due to application of AP5 (Fig. 2*A*, *2*); evoked activity in the time interval 30-150 msec was inhibited to a significantly lesser extent (*A*, *3*). The next example (Fig. 2*B*) also shows AP5-induced reversible inhibition of background activity (*B*, *2*) and evoked activity during time periods characteristic of components *II* (30-200 msec; Fig. 2*B*, *3*) and *III* (200-400 msec; *B*, 4). The features of the cumulative histograms in Fig. 2*A*, *9*, and Fig. 2*B*, *9* show that there were no systematic differences in the rates of accumulation of changes in the instantaneous frequency of evoked activity from the mean background level before, during, or after exposure to AP5; therefore, changes in responses observed on exposure to AP5 are entirely due to inhibition of background activity. The distribution of movement markers in rows shown in Fig. 2*B*, *1* and in the histogram for movement latent periods (*B*, *5*) show that microapplication of AP5 delays the onset of movement.

Figure 3*A* shows an example of a reduction in neuron activity due to AP5 without a statistically significant change in background activity (*A*, *2*). A reduction in the rate of accumulation of changes in the frequency of evoked discharges from baseline can be seen by comparing the cumulative histograms in Fig. 3*A*, *9*. AP5 decreased activity in the initial period (50-200 msec; Fig. 3*A*, *3*) and reduced the peak response (250-450 msec; Fig. 3*A*, *4*). Figure 3*A*, *5* also shows a reversible increases in the latent period of the paw movement response.

An example of a neuron without background activity is shown in Fig 3*B*. AP5 inhibited component *II* (30-150 msec; Fig. 3*B*, *3*) and increased the latent period of the motor response (*B*, *5*); component *III* (150-400 msec) was slightly increased in this case (*B*, *4*).

Only component *II* was clearly demarcated in the responses of the neurons shown in Fig. 4; these correspond in shape to the example shown in Fig. 1*B*, *7*. In both cases, AP5 inhibited responses (Fig. *4*, *3*) without notable change in background activity (*2*), and increased the latent period of movement (*5*).

The example shown in Fig. 5*A* shows that AP5 inhibited the initial phase of the neuron response (at 70-220 msec, characteristic of component *II*; Fig. 5*A*, *3*), while phase *III* (250-500 msec) did not change significantly (*A*, *4*). AP5 increased the latent period of the movement response (*A*, 5). Repeated application of AP5 (Fig. 5*B*) produced essentially the same changes, consisting mainly of a reduction in the initial phase of the neuron response (90-210 msec; Fig. 5*B*, *3*). After correction for the trend, there was an increase in the latent period of the motor response (*B*, *5*).

General Data on the Effects of AP5 on Neuron Activity and Motor Responses. Microiontonphoretic application of AP5 inhibited both background and evoked neuron activity in the motor cortex. Reversible (i.e., the discharge frequency during application was statistically significantly different from the frequency both before and after application) reductions in background activity on exposure to AP5 were seen in 35 of 76 recordings (46%) of spontaneously active neurons. There were no cases of increases in the background activity frequency.

Of 63 neurons whose responses yielded a component *I*, this was inhibited by AP5 ($p \leq 0.05$) in four cases (about 6%), while increases were seen in only one case. The probability that 4 or more rare ($p = 0.025$) events of the same sign would occur in 63 trials is $p > 0.05$ (since we are dealing here with one-directional changes, the probability of a given event is taken as 0.025); therefore, there is insufficient basis to consider motor cortex neuron response component *I* to change on application of AP5.

Changes in evoked activity limited to the time period 30-70 msec $< T <$ 150-240 msec (depending on the form of particular PSH), i.e., the time at which response component *II* is generated, were assessed in 73 cases. Reversible inhibition was seen in 32 cases (44%), while reversible stimulation occurred in three cases (4%). The probability that three or more rare ($p = 0.025$) events of the same sign would occur in 73 trials is $p > 0.05$, so cases of increases in component *II* during exposure to AP5 can be ignored. Of 32 cases in which statistically insignificant reductions in response component *II* were seen, the difference between the size of component *II* and background activity decreased in 28 cases and increased in only 4 cases ($p < 2 \times 10^{-5}$, criterion of signs).

Reversible inhibition of response component *III* was seen in 11 of 61 cases (18%, $p < 5 \times 10^{-4}$), and enhancement occurred in one case. Inhibition of component *II* occurred significantly more frequently than inhibition of response components *I* ($p < 1 \times 10^{-5}$) and *III* ($p < 1 \times 10^{-3}$) (criterion for relative frequency comparisons [3]).

Statistically significant increases in the latent periods of motor responses were seen in 14 of 74 cases (about 19%, $p \approx 0$), and inhibition was seen in only 1 case.

Thus, increases in individual components of the responses of motor cortex neurons and shortening of the movement latent period on application of AP5 were seen very rarely, and the proportion of such events was no greater than would be expected from the random spread of the data.

DISCUSSION

The results obtained here and previously [6-8] show that performance of a conditioned reflex consisting of placing the forepaw on a support produces in the cat motor cortex not only an increase in neuron frequency associated with paw elevation, but also two types of response associated with the stimulus, in this case of the parietal cortex: a primary response consisting of a short burst of activity with a minimal latent period (LP_{min}) of several milliseconds and a latent period to the peak (L_{peak}) of 10 ± 7 msec, and duration (*T*) of no more than 30-50 msec, and a secondary burst of activity ($LP_{min} \geq 20$ msec, $LP_{peak} = 65 \pm 18$ msec, $T \leq 200$ msec). The excitatory responses of nerve cells corresponded to negative displacement of the focal potential, here termed *N*1 and *N*2, whose peak latencies coincided with the mean values of LP_{peak} for the spike responses.

Microapplication of AP5, a specific competitive blocker of glutamate NMDA receptors, to the neurons of interest showed that the primary response (*I*) to electrical stimulation of the parietal cortex was not sensitive to AP5, and was then generated by activation of non-NMDA receptors; AP5 significantly inhibited component *II* and, to a lesser extent component *III* of the response, indicating a role for NMDA receptors in their origin.

Studies carried out on frontal cortex sections [23-25] have described two types of excitatory postsynaptic potentials (EPSP) arising in response to intracortical stimulation: rapid monosynaptic NMDA-independent EPSP (LP_{min} = 2-3 msec, $LP_{peak} = 8.6 \pm 4.2$ msec, T = 30-60 msec) and longer-latency NMDA-dependent EPSP, which appear when the stimulus current is increased slightly as long as it remains below the threshold for spike generation ($LP_{peak} = 40 \pm 11$ msec; $T = 130 \pm 26$ msec).

Comparison of the responses of neurons in frontal cortex sections with responses to conditioned stimuli in the motor cortex of conscious cats showed that response *I* appears to reflect rapid EPSP evoked by activation of non-NMDA glutamate receptors during stimulation of the direct projections of field 5 to the motor cortex [9, 12]. The secondary spike responses have the same AP5 sensitivity and similar time parameters with long-latency NMDA-dependent EPSP.

NMDA receptors in the cortex are mainly located on pyramidal dendrites, around the endings of horizontal excitatory connections: cortico-cortical axons and axon collaterals from neighboring pyramidal cells [14, 17, 18, 21, 27]. It can therefore be suggested that the secondary burst of motor cortex neuron excitation in response to the conditioned signal is generated by activation of NMDA receptors associated with the endings of parieto-frontal projections and/or endings of return collaterals of neighboring pyramidal neurons. Passage of groups of spikes through return collaterals, with a total duration of 30-50 msec, which corresponds to response *I*, must increase the duration of the peak latent period of secondary NMDA-dependent responses in the cortex of the conscious cat as compared with values recorded in cortex slices. Adding 30 msec to the time parameters of long-latency EPSP as reported in [23-25] gives LP_{peak} = 70 msec and T = 160 msec, which virtually coincides with the values obtained here.

Component *III* of the motor cortex neuron response correlates directly with paw movement. Analogous responses were recorded in the *VL* nuclei of the thalamus — the thalamic projection nucleus for the motor area of the cortex [20]. The fact that thalamocortical endings are not directly connected with NMDA-type receptors [17, 21, 27] explains the lower sensitivity of component *III*, as compared with component *II*, to application of AP5.

A characteristic effect of AP5, observed along with inhibition of secondary excitatory responses, was inhibition, often very significant, of prestimulus ("background") activity. Inhibition of the background activity of cortex neurons by AP5 has also been reported in other investigations [10, 15]. Inhibition of background activity by NMDA blockers could be due to the high concentration of free glutamate in the fluid surrounding central neurons [22]. It follows from this that the mean level of

motor cortex neuron depolarization in the conscious cat, in a state of motor readiness, is significantly greater than the activation threshold of ion channels controlled by glutamate NMDA receptors (about −70 mV [13]), and that the activity of this receptor-channel complex plays an important role in controlling cortical neuron excitability in the conscious animal.

CONCLUSIONS

The results presented here and previously [6-8] show that performance of a conditioned reflex in which a cat places a paw on a support is associated with the appearance in the contralateral motor cortex of movement-associated excitatory responses as well as two additional types of response, associated with the stimulus. Short-latency rapid (latent periods about 10 msec, duration up to 30-50 msec) responses had low sensitivity to blockade of glutamate NMDA receptors; later and longer-lasting responses (peak latent period 65 msec, duration up to 150-200 msec) were significantly inhibited by the NMDA receptor blocker AP5. These responses have identical AP5 sensitivity and similar time parameters as the two types of EPSP recorded in frontal cortex slices in response to intracortical stimulation [23-25]. A third component of the motor cortex neuron response, associated with limb movement, developed parallel with and under the influence of activity of neurons in the *VL* nucleus of the thalamus [20]. The lower sensitivity of the third component to AP5, as compared with the second component, can be explained in terms of the absence of NMDA receptors in the endings of thalamocortical connections [17-21].

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