QUANTAL ANALYSIS OF LONG-TERM POSTTETANIC CHANGES IN MINIMAL POSTSYNAPTIC POTENTIALS OF HIPPOCAMPAL SLICES IN VITRO

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Minimal excitatory postsynaptic potentials (EPSP) were investigated in 13 neurons under single or double-pulse near-threshold microstimulation of the radial layer (Schaffer's collaterals) and stratum oriens in surviving hippocampal slices (area CA1) in guinea pigs. The amplitude of 23 EPSP (9 units; 12 pathways) rose after tetanization of Schaffer's collaterals over a 5-55 min period, taken as long-term potentiation (LTP). Statistical analysis conducted using four methods of quantal hypothesis based on a binomial approximation revealed an increase in mean quantal content (m) during LTP. The rise in quantal size was only statistically significant when using data obtained from a section of these methods (mainly for stretches of over 15 min following tetanization) and shows no correlation with intensity of LTP. The pronounced rise in m demonstrated using different methods matches data from experiments on intact animals and indicates a presynaptic location of the mechanisms underlying protracted persistence of residual tetanization lasting some tens of minutes.

INTRODUCTION

Use of quantal hypothesis techniques [2, 3, 8] makes it possible to locate mechanisms of synaptic plasticity. Using quantal hypothesis, we can write the mean amplitude of excitatory postsynaptic potentials (EPSP) as

$$E = m \cdot v, \tag{1}$$

where v stands for quantal size (shift in membrane potential induced by release of one quantum of transmitter) and m for mean quantal content (mean number of quanta released due to the arrival of one presynaptic impulse):

$$m = n \cdot p, \tag{2}$$

where n and p are binomial parameters reflecting the number of transmitter release sites and the likelihood of joint operation of a single release site producing release of a single quantum, respectively [19]. We have already used quantal hypothesis for analyzing the mechanism of long-term potentiation (LTP) in the hippocampus, regarded as a model for memory [3, 4, 16, 26, 28, 29]. A rise in m with no change in v for up to 12 min after tetanization was noted in recordings of minimal EPSP (those induced by near-threshold microstimulation of afferent fibers) in area CA3 in rabbits [3, 4, 27, 28]. According to quantal hypothesis, this implies a presynaptic location of the mechanisms underlying LTP. Subsequent analysis of findings obtained in hippocampal slices, enabling longer intracellular recording to be made, confirmed this conclusion for a 15-45 min period after tetanization [8]. At the same time, a rise in v was also shown using one of the analysis techniques [8]. In this study, we recorded minimal EPSP and compared quantal parameters corresponding to initial and later periods following tetanization (5-15 min and 16-55 min, respectively) in order to clarify the mechanisms of LTP. Several shortcomings of previous research were dispensed with [8] and additional techniques of analysis used [5].

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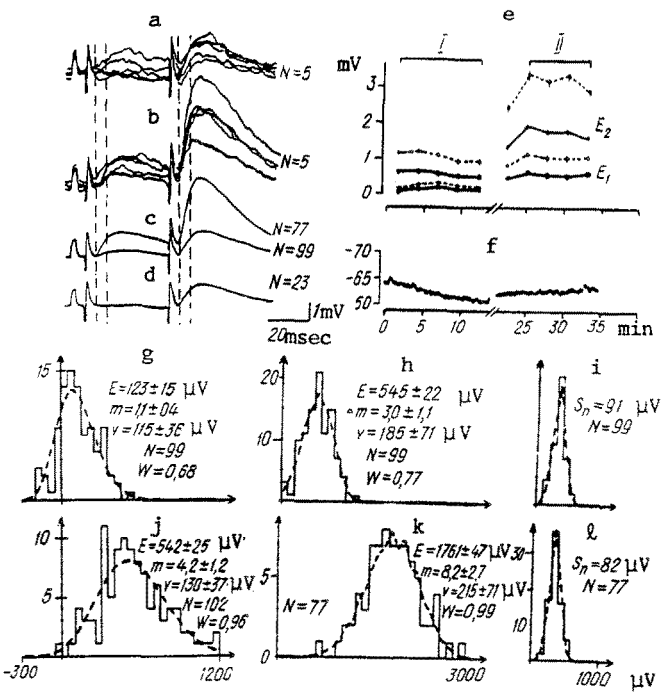

Fig. 1. Sample hippocampal EPSP and their statistical analysis using histogram techniques. a, b) Response to presentation of double-pulse stimuli before (a) and after (b) tetanization. Calibrating impulse (amplitude 1 mV) given at start of traces; c) superposition of average responses before and after tetanization; d) averaging of events with fading out in response to presentation of first stimulus in each pair prior to tetanization; e) change in time in mean amplitude of EPSP induced by presentation of first (E_1) and second (E_2) test stimuli in the same experiment. Abscissa: time after start of recording, min; ordinate: amplitude (dotted lines) and "mean amplitude of window" (indicated by continuous lines), calculated from 20 consecutive measurements, mV. Vertical dashes, standard error; I, II: quasi-steady-state portions before and after tetanization, respectively; f) alteration in membrane potential (ordinate, mV) during trial. Abscissa: same as d; g-ℓ) experimentally obtained distribution of EPSP amplitude and that obtained theoretically (columns and dashed lines, respectively – g, h, j, k), and calibrating impulse (i, ℓ) before and after tetanization (g-i and j-ℓ respectively). Abscissa: EPSP amplitude, μV; ordinate: number of events. Parameters calculated using histogram method, estimating standard error, and establishing maximum likelihood of zero hypothesis according to Wilcoxon's χ^2 test.

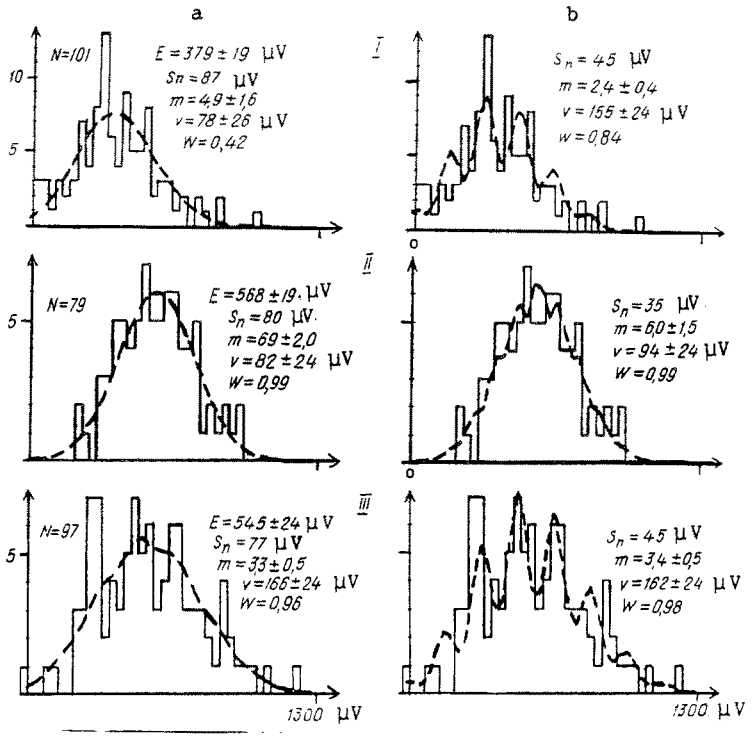

Fig. 2. Two procedures for seeking the best fit between theoretical and experimental distribution (compared); a) finding v_1 with S_n calculated from experimental data; b) finding optimum v_1 and S_n. Distribution of EPSP amplitude before (I) and after (II, III) tetanization. Significance of abscissa, ordinate, and other notations as for Fig. 1g-ℓ.

METHODS

The techniques used were similar to those already described elsewhere [3, 5-8, 17, 21]. This study was conducted on guinea pig hippocampal slices. Glass microelectrodes for recording (potassium acetate; resistance 20-100 MΩ) were inserted into the CA1 pyramidal layer, and the stimulating electrode (tungsten in glass insulation, 0.1-1.0 MΩ) penetrated the radial layer (and sometimes stratum oriens). The tests consisted of single or paired stimuli with an interval of 40-50 msec repeated every 8-10 sec; amplitude (0.7-1.6 V) and duration (20-40 μsec) were so chosen that single stimulus presentation induced minimal EPSP of less than 1 mV in amplitude with response to a proportion of stimuli fading out (Fig. 1a). Tetanization at the rate of 100 Hz consisted of 10 stimulus trains of 200 msec duration (interval between trains 8-10 sec). Duration of stimuli was increased 2-4-fold for tetanization.

Potentials were recorded by computer and processed once experiments had ended. The recording band measured from 0 to 300 Hz so as to reduce standard deviation of noise (S_n). "Mean amplitude of the window" was used to estimate level of EPSP [17]. Measurement of the latter (equivalent to its area) will be referred to as "amplitude" for simplicity's sake. Control measurements showed a high degree of correlation between this parameter and amplitude at a fixed point in time (Fig. 1e, dotted line). The "window" for measuring (of 4-10 msec) was selected according to average response to presentation of the first stimulus in a pair (Fig. 1a-d, dashed line) between start of EPSP and the point on the rising front 0.5-3.0 msec before maximum level. Near-threshold stimulation and means of measurement reduced the potential effect of postsynaptic and inhibitory potentials. Control averaging of depressions never produced significant hyperpolarization during the interval corresponding to the "window" (Fig. 1d). A graph was produced plotting amplitude against serial number of stimulus (Fig. 1e), and quasi-steady-state portions were identified [3, 8, 17], within which the means of 20 measurements did not differ significantly ($p > 0.05$; Student's t test used here and subsequently). Sections were chosen for control prior to tetanization (I – Fig. 1d, Fig. 2, Fig. 5), for neurons 5-15 (II – see Fig. 1d, Fig. 2, and Fig. 5), and 16-55

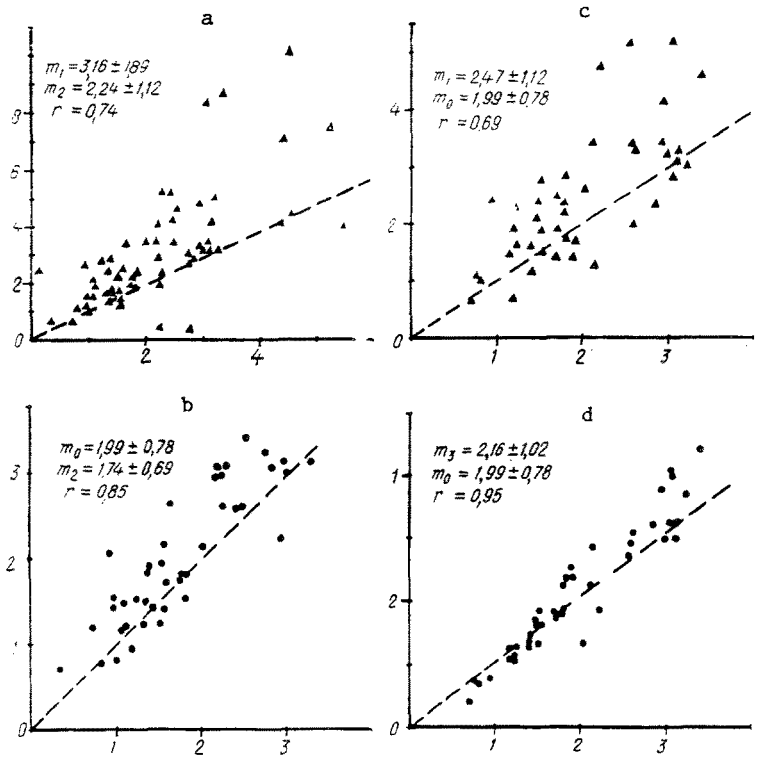

Fig. 3. Correlation between values of quantal content estimated by various methods. Abscissa: m_2 (a and b) and m_0 (c and d); ordinate: m_1 (a and c), m_0 (b), and m_3 (d). Dashed lines pass through data points with abscissa and ordinate marked off in equal values. Mean values shown (± standard deviation) and correlation coefficients (r).

min after tetanization (III – Fig. 2 and 5). For each section containing between 59 and 119 measurements (average 88) the number of depressions was established (N_0); the latter was determined by two observers and verified by averaging responses taken as depressions (Fig. 1d). Four methods of determining quantal parameters based on a binomial distribution have already been described in our previous study [5]. Parameters calculated by means of histograms based on selection of a theoretical distribution close to that found experimentally will be indexed as 1; those arrived at using a coefficient of variation, as 2; those based on depression, as 0; and those in which a combination was used, as 3.

RESULTS

For not less than 15 min after tetanization, EPSP were recorded in 13 neurons without spontaneous firing and with an absolute membrane potential level of not less than 60 mV (Fig. 1f). In 9 units from which readings of 23 EPSP were obtained (single or paired stimulation of 11 inputs before and after 10 instances of tetanization), a significant rise in E on sections II (Fig. 1a-c) and III was observed ($p < 0.01$). This increase will henceforth be referred to as BF. Level of BF (i.e., the relationship between E before and after tetanization) measured between 118 and 441%; see Fig. 5 for mean levels of this parameter. "Basic" (m, v) and binomial parameters (p, n) were calculated for each section. A histogram-based method was used in two variations (see Fig. 2) taking potential change in noise level during EPSP into account. The value of S_n calculated by direct measurement of noise or calibrating impulse was used in the first of these (Fig. 1i-ℓ and Fig. 2a) in finding v_1. The second variation (Fig. 2b) involved seeking optimum values of both v_1 and S_n. The program produced model (theoretical) distributions closest to those found experimentally with both variations in all cases except one ($p > 0.1$, in most cases $p > 0.5$ – see value of w in Figs. 1 and 2). In 58 out of 65 instances, the similarity between experimental and theoretical distributions obtained on the basis of the second variation was greater (see a and b in Fig. 2). The level of S_n determined using the second variation was significantly lower than the S_n obtained by measurement (60 ± 33 and 69 ± 29 μV, respectively, $p < 0.005$), although average parameters and measurements of these did not differ, on the whole, after tetanization.

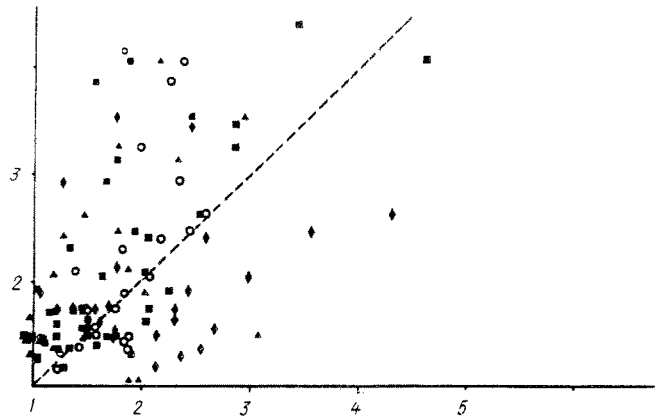

Fig. 4. Level of long-term potentiation (ordinate – ratio between mean amplitudes for posttetanic sections and control amplitudes) plotted aginst changes in m (abscissa – ratio between m calculated using four methods after tetanization and control levels of m). Triangles; data obtained by histogram method where $v_1 > S_n$; squares, by coefficient of variation method; circles, by method of elimination; diamonds, by a combined method.

Correlation between parameters calculated on the basis of histograms and those obtained using other methods did not rise significantly; results from using the first variation will therefore be given below. It has already been found [5] that the histogram method does not allow parameters at $S_n > v$ to be determined [5]; the case $v_1 > S_n$ will therefore be examined separately. Determining m_1 was also most reliable in nearly all such cases; these values were more than three times greater than the error of calculating m_1 ($m_1 > 3S_m$).

Parameters calculated using different methods (23 and 40 sections before and after tetanization, respectively) could differ in some individual cases but were generally similar (see Fig. 3 and Table 1). A significant correlation was seen between parameters m and v determined using various methods (Fig. 3). Correlation of binomial parameters was usually poorer and sometimes insignificant ($r = 0.70$ for p_1 and p_2, for instance and $r = 0.24$ for p_2 and p_3). Generally speaking, the most easily reproducible posttetanic change for all methods used (see Table 1) was a rise in m. This effect was found in 27 out of 39 posttetanic sections, and in 23 out of 25 sections. Mean value of m_1 after tetanization equaled 166 ± 131% of control level (difference from 100% significant, $p < 0.005$; Wilcoxon's two-tailed t test used here and subsequently). An even greater increase in m_1 occurred for more "reliable" cases ($v_1 > S_n$), especially for section II (see Fig. 5, indicated by triangles). The rise in m_2 could be even more reliably produced (in 38 out of 40 sections) together with m_0 and m_3, which increased in all cases (see Table 1 and Fig. 5). A more significant correlation ($p < 0.005$) was seen between the relative values of E and m as determined using all methods (Fig. 4) and each individually. At the same time, it will be seen from Fig. 4 that a large proportion of values (apart from m_3) are found to the left of the straight line bisecting the right angle (indicating a rise in v). An example of one case in which, using the histogram method, LP may be treated as just the result of a rise in v can be seen in Fig. 2a, I, III. The greatest rise in v_1 took place with $v_1 < S_n$ for control sections, however. In those cases where $v_1 > S_n$, the increase in v_1 was only significant for sections more than 15 min after tetanization (Table 1 and Fig. 5). A similar result was obtained using the phasing-out technique (see Table 1). The rise in v_1 did not correlate with raised EPSP for all data ($r = -0.17$, $N = 39$, $p > 0.29$) nor in cases with $v_1 > S_n$ ($r = -0.08$, $N = 25$, $p > 0.7$). Conversely, moderate changes in v_2 and v_0 (Fig. 5) revealed a correlation with the level of LP ($p = 0.47$ and 0.82, respectively). A significant correlation was also observed between changes in E and v_3 ($p = 0.63$: $p < 0.005$), although the mean value of v_3 remained virtually unchanged (see Table 1).

The mean values of binomial parameters p and n before and after tetanization are shown in Table 1. For those cases where $n_1 > 25$ (and p_1 less than error of measurement), n_1 and p_1 were viewed as undefined (Poisson's distribution) and were not included in Table 1. It will be seen from Table 1 that binomial parameters usually rose after tetanization, although this may be taken as just a preliminary quantitative estimate (see below).

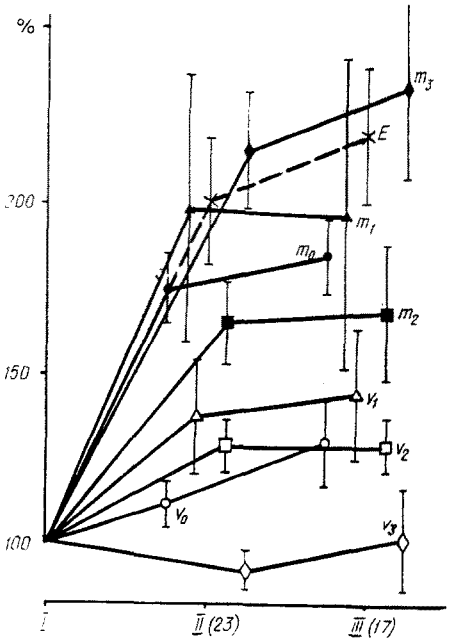

Fig. 5. Changes in mean amplitude of EPSP (E), mean quantal content (m_1, m_2, m_3, and m_0), and quantal size (v_1, v_2, v_3, v_0) after tetanization. Values calculated for control portion prior to tetanization taken as 100% (data point I on horizontal axis). Values calculated for posttetanic sections (data points II and III on horizontal axis) expressed as percentages of control level and expressed in the form of mean ± standard error. Data where $v_1 > S_n$ used for histogram method. Number of measurements for E, m_2, and v_2 shown in brackets. Detailed explanations given in the text and Table 1.

DISCUSSION

This study differed from previous research [3, 4, 8, 27, 28] in comparing quantal parameters during two prolonged periods of tetanization using updated techniques. Fundamentally, results resembled those obtained earlier in experiments on intact animals [3, 4, 27, 28], and in research on hippocampal slices while taking readings of combined EPSP [8]. The rise in m correlated with the degree of LP would imply that presynaptically located mechanisms underlie the rise in synaptic efficacy during LP.

At first sight, the primarily presynaptic mechanisms of LP so deduced appeared to contradict findings on the effect of postsynaptic action on the formation of LP [6, 16, 22-24]. This contradiction can be dispelled by postulating a variation in the conditions of LP induction (including postsynaptic depolarization and increased intracellular Ca^{2+} concentration) and in mechanisms for preserving residual LP (mainly an increase in transmitter release). On the other hand, we also detected a rise in v, pointing to possible involvement of postsynaptic mechanisms. This correlates with findings from electron microscope research into postsynaptic transformation following tetanization [16]. Application of a proportion of the methods adopted showed a rise in v occurring mainly at a considerable time after tetanization. This fits in with the recently obtained finding [13] of delayed increased sensitivity to quisqualate. It should be specially mentioned, however, that we observed a rise in m in all cases, so that possible postsynaptic changes may serve to explain only a limited part of LP (Fig. 5). The more significant rise in v revealed using the histogram method does not correlate with the degree of LP and cannot be reproduced for the most significant instances where $v_1 > S_n$. Our findings overall indicate a primarily presynaptic location of mechanisms for preserving residual LP with possible involvement of postsynaptic mechanisms.

We adopted a "simple" binomial model postulating equality of p for all transmitter release sites, in common with most other writers [2, 3, 18]. An automated histogram technique does not in itself provide a test for the validity of this hypothesis [8]. Model distributions fitted in satisfactorily with those found experimentally according to the χ^2 test in nearly all cases (see values of w in Figs. 1 and 2). The binomial model based on parameters calculated using other methods cannot be rejected either: in Fig. 1g, h, j, and k, significance level for parameters relating to the histogram method equaled 0.68-0.99 as compared with 0.53-0.83 for those associated with the coefficient of variation method. Other more complex models taking account of variations in p also exist [1, 9, 30]. However, application of these is considerably more demanding with respect to sample size and noise level – usually incompatible with maintaining a steady state in control and posttetanic amplitudes (it should be mentioned that the subject of steady state is often neglected in the literature). At this stage of our research we confined ourselves to a "simple"

TABLE 1. Mean Values (± Standard Deviation) of Quantal Parameters of Minimum Hippocampal EPSP before Tetanization (I), 5-15 min after Tetanization (II), and 16-55 min after Tetanization (III)

Method	Section	N	Quantal parameters			
			m	v, μV	p	n
Histogram	I	22	2,89±2,34	97±45	0,41±0,13	5,5±3,9 (10)
	II	23	3,32±1,66	144±68	0,53±0,11*	6,4±3,4 (16)
	III	17	3,33±1,55	152±73	0,50±0,16	6,0±1,6 (11)
Histogram ($v_1 > S_n$)	I	14	2,00±1,07	118±45	0,41±0,13	5,5±3,9 (10)
	II	23	3,32±1,66**	144±68	0,53±0,11*	6,4±3,4 (16)
	III	12	2,81±0,74*	178±71*	0,50±0,16	6,0±1,6 (11)
Coefficient of variation	I	23	1,70±0,98	143±51	0,46±0,11	3,6±1,1 (22)
	II	23	2,50±1,11***	181±73**	0,54±0,11***	4,4±1,4***
	III	17	2,60±1,10***	191±81**	0,52±0,09*	4,8±1,3***
Elimination	I	20	1,62±0,74	133±64	0,44±0,08	3,8±1,3
	II	14	2,25±0,67**	137±73	0,49±0,07**	4,5±1,2*
	III	11	2,34±0,68**	164±85*	0,49±0,07*	4,8±0,9*
Combined	I	20	1,66±0,96	143±83	0,53±0,12	2,8±1,6 (11)
	II	14	2,57±0,82**	128±85	0,46±0,12	5,9±4,1*(7)
	III	11	2,55±0,82**	153±84	0,45±0,09	5,5±1,9* (8)

Note. Corresponding values for amplitude: 241 ± 157 (section I), 461 ± 341*** (section II), and 485 ± 253** (section III) μV. *, **, *** denote significant increase compared with controls prior to tetanization ($p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively: Wilcoxon's two-tailed t test). Number of measurements for p and n shown on right in brackets when lower than for m and v; N: number of EPSP.

binomial model taking account of the N and S_n values obtained, the absence of major discrepancies with the model, and the fact that identifying alterations in m and v was the main purpose of our research. Estimation of p and n can be considered the most approximate factors under the present conditions; they serve the purposes of illustration. It should also be mentioned that both the decline in the coefficient of variation and the number of lapses following tetanization would point to a perceptible rise in m, irrespective of type of model (whether "binomial" or complex).

Certain data, however [6], would suggest the presence of ineffective synapses which possibly become effective following tetanization. It has already been noted [3, 4, 28] that changes in m where initially ineffective synapses exist require cautious interpretation. Ineffective synapses making no noticeable contribution to pretetanic EPSP may indeed increase in efficacy due to both pre- and postsynaptic reorganization. Our findings indicate that, under these circumstances, mean efficacy of a single quantum of transmitter for hypothetical "new" synapses must resemble quanta for initially effective synapses, while sensitivity of subsynaptic receptors and other postsynaptic factors do not change significantly during LP. At the same time, it should be mentioned that the standard explanation — of a rise in the number of quanta released where a single presynaptic impulse arrives — is the most favored; it is also confirmed by the result of measuring the amount of transmitter released [12, 15, 25] and Ca^{2+} uptake [10], as well as quantal analysis of alterations in EPSP occurring in hippocampal area CA3 neurons after introduction of phorbol esters [31] and long-term postactivation changes at peripheral synapses [11, 20] in central mollusk neurons [14].

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PLASTIC SYNAPTIC REORGANIZATION IN THE SENSORIMOTOR CORTEX OF ADULT CATS AFTER LESIONING OF THE CONTRALATERAL CEREBELLAR NUCLEUS INTERPOSITUS

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Intact cats and animals undergoing lesioning of the contralateral cerebellar nucleus interpositus between one and six months previously were used in this research, employing intracellular recording techniques and investigating the response of corticospinal neurons (CSN) to stimulating the aforementioned nucleus, the ipsilateral cerebellar nucleus interpositus, and the ventrolateral thalamic nucleus. A reduction was found in the stage of rise to peak in monosynaptic thalamocortical EPSP in CSN of operated animals, with a low axonal conduction velocity, pointing to distant terminal dendrosomatic sprouting and formation of new synapses at proximal sections of the CSN somatodendritic membrane. Findings are presented on formation of ipsilateral interpositothalamocortical projections duplicating similar contralateral projections in intact animals. Contralateral cortico-interpositol collaterals were found in intact animals and similar sprouting of ipsilateral origin in those which had undergone surgery.

INTRODUCTION

Destruction of the cerebellar nucleus interpositus (CNT), seen as a stimulus for manifestation of standard reorganization in interposito-rubral projection from the contralateral side, was successfully used in experiments involving recording of electrical activity in red nucleus neurons, thus providing a description of ipsilateral interposito-rubral collateral axonal sprouting with formation of "functional synapses" in the red nucleus [6, 9-11]. Renewal of projection was discovered by the writers cited, mostly in immature cats (at the early postnatal developmental stage) in view of the wide extent of collateral arborization, however. As regards terminal corticorubral sprouting, this is also characteristic of adult animals [1, 8]. Our previous research [5] revealed the possibility of ipsilateral interposito-rubral collateral sprouting occurring as well as new synapses after lesioning of the contralateral NI (cNI) in adult cats. Formation of recurrent rubro-interpositol collateral branching was also described following a feedback pattern on the side of plastic reorganization of interposito-rubral projection similar to that found by ourselves on the contralateral side in intact animals [2, 4]. Ipsilateral rubral-interpositol projection was recognized as responsible for the certainty that an ipsilateral interposito-rubral connection would be re-established. The existence of this same connection does not

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