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Synaptic Dynamics on Different Time Scales in a Parallel Fiber Feedback Pathway of the Weakly Electric Fish

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Lewis, John E. and Leonard Maler. Synaptic dynamics on different time scales in a parallel fiber feedback pathway of the weakly electric fish. \textit{J Neurophysiol} 91: 1064–1070, 2004. First published November 5, 2003; 10.1152/jn.00856.2003. Synaptic dynamics comprise a variety of interacting processes acting on a wide range of time scales. This enables a synapse to perform a large array of computations, from temporal and spatial filtering to associative learning. In this study, we describe how changing synaptic gain via long-term plasticity can act to shape the temporal filtering of a synapse through modulation of short-term plasticity. In the weakly electric fish, parallel fibers from cerebellar granule cells provide massive feedback inputs to the pyramidal neurons of the electrosensory lateral line lobe. We demonstrate a long-term synaptic enhancement (LTE) of these synapses that is biochemically similar to the presynaptic long-term potentiation expressed by parallel fibers in the mammalian cerebellum. Using a novel stimulation protocol and a simple modeling paradigm, we then quantify the changes in short-term plasticity during the induction of LTE and show that these changes can be explained by gradual changes in only one model parameter, that which is associated with the baseline probability of transmitter release. These changes lead to a shift in the spike frequency preference of the synapse, suggesting that long-term plasticity is not only involved in controlling the gain of the parallel fiber synapse, but also provides a means of controlling synaptic filtering over multiple time scales.

INTRODUCTION

The synapses from parallel fibers to Purkinje neurons in the cerebellum exhibit multiple forms of synaptic plasticity, on various time scales and with both pre- and postsynaptic loci (Hansel et al. 2001). Presynaptically, there is short-term plasticity, with time scales of milliseconds (Dittman et al. 2000), as well as long-term potentiation (LTP), with time scales of hours (Salin et al. 1996). The presynaptic LTP is mediated by a cAMP/ PKA-dependent pathway, and results in changes to paired-pulse facilitation that are consistent with an increase in the baseline probability of transmitter release (Castillo et al. 2002; Chen and Regehr 1997; Jacoby et al. 2001; Salin et al. 1996). Release probability also plays an important role in short-term plasticity, for instance by influencing the balance between facilitation and depression (Dittman et al. 2000). Thus there is the potential for interaction between different mechanisms of plasticity at very different time scales, but the functional implications of such interactions are not clear. To begin to understand the role of parallel fiber synapses in processing dynamic signals, a quantitative description of these interactions is necessary.

In the weakly electric fish, cerebellar granule cells provide parallel fiber inputs to the electrosensory lateral line lobe (ELL). The ELL is the first way station in the neural pathways involved in the electric sense of these fish—a sense that is critical for prey capture and conspecific communication (Helleligenberg 1991). The parallel fibers provide feedback input via synapses onto apical dendritic spines of ELL pyramidal neurons (Maler et al. 1981). These synapses exhibit a number of overlapping forms of synaptic plasticity over time scales of milliseconds to hours (Bastian 1998; Han et al. 2000; Lewis and Maler 2002) and are necessary for effective electrosensory function (Bastian 1986). Further, they express adenylyl cyclase and PKA (Maler 1999) and are thus similar to mammalian cerebellar parallel fibers at many different levels.

In this study, we investigate the effect of long-term plasticity at the ELL parallel fiber synapse, lasting tens of minutes, on its short-term dynamics lasting tens of milliseconds. We first demonstrate a long-term enhancement (LTE) of this synapse that is similar to the cAMP/PKA-dependent presynaptic LTP observed in the mammalian cerebellum (Salin et al. 1996). The novelty in our approach relates to the stimulation protocol used to induce LTE. We use multiple repetitions of a random stimulus train to induce LTE and then fit a simple synaptic model (Lewis and Maler 2002) to the evoked responses. This method provides a characterization of short-term synaptic dynamics during the induction of LTE that is more accurate than that achieved using standard paired-pulse stimulation protocols. Our results show that a progressive change in release probability can explain the experimentally observed changes in short-term dynamics during LTE induction. Further, pharmacological conditions that occluded LTE also blocked the progressive change in our estimate of release probability, thus confirming the reliability of our analyses. An analysis of our model over a range of input frequencies suggests that changing the baseline probability of release, and thus the steady-state gain of the synapse, also provides a means of systematically changing the temporal filtering properties of the parallel fiber synapse.

METHODS

ELL slice preparation

The gymnotiform fish \textit{Apterobatus leptorhynchus} (male or female, 10–15 cm in length) were anesthetized in oxygenated water containing 0.2% 3-aminobenzoic ethyl ester (MS-222, Sigma). Surgical procedures and slice preparation were performed as previously described (Berman and Maler 1998; Lewis and Maler 2002). Briefly, true-
transverse 350-μm slices of the ELL were obtained and transferred to an interface-type slice chamber. Slices were perfused (2 ml/min with bubbled (95% O₂-5% CO₂), room-temperature (20–22°C), artificial cerebrospinal fluid (ACSF) containing (in mM) 124 NaCl, 24 NaHCO₃, 10 d-glucose, 1.25 KH₂PO₄, 2 KCl, 2 CaCl₂, and 2 MgSO₄. A recovery period of 1–2 h was allowed before recordings were made. All pharmacological agents were bath applied. Stock solutions of Forskolin (FSK) and H-89 (Sigma) were prepared in DMSO and diluted in ACSF (to 10 and 0.2 μM, respectively) such that the final concentration of DMSO was <0.1%. All protocols were approved by the University of Ottawa Animal Care Committee.

Electrophysiological methods

Stimulation and recording methods were similar to those described previously (Lewis and Maler 2002). Parallel fibers in the ELL dorsal molecular layer (DML) were stimulated through a stimulus isolation unit (Digitimer Ltd; 100-μs pulses, 10–25 V) using two glass micro-electrodes (tip size approximately 10 μm) in a bipolar configuration, oriented perpendicularly to the parallel fibers, about 100 μm apart. Field potential recordings of the synaptic responses to stimulus trains were made using glass microelectrodes (5–10 MΩ filled with 1 M NaCl). The electrode tips were placed in the DML of the centromedial segment of the ELL at a depth of 30–60 μm and along the parallel fiber axis, medial to the stimulation site. Recordings were amplified and filtered (DC-1 kHz, Axoclamp-2A, Axon Instruments), digitized at 5 kHz (ITC-16, Instrutech Corporation, Greatneck, NY) and acquired using Pulse Control (Instrutech Corporation) and Igor Pro (WaveMetrics, Lake Oswego, OR) software running on a Power Macintosh 7100. We quantified the synaptic field potentials by measuring the peak deflection from baseline. The baseline was taken as the average potential in a 2-ms window just prior to stimulus onset.

The stimulation protocol (5-train protocol) used in our study consisted of five repeats of the same 200-pulse train with 5 s between each repeat. The 200 stimulus pulses within the train were separated in time by randomly distributed intervals (Poisson stimulation) with a mean interval of 62.5 ms (16 Hz mean frequency). The random intervals were computer-generated from an exponential distribution that was truncated to have a minimum interval of 10 ms (intervals smaller than this interfered with the measurement of the synaptic response). In the short term (<2 s), a mean stimulation frequency of 16 Hz results in minimal recruitment of the disynaptic inhibitory component of this feedback pathway (Lewis and Maler 2002). For 5 min before and 5 min after each train protocol, paired-pulse test stimuli were delivered every 30 s with an interpulse interval of 40 ms (for a total of 10 paired-pulse trials before and after train stimulation). The measure of synaptic efficacy was taken from the response to the first of this pair of pulses. The data reported for the test stimuli are the averages of two trials during a given minute. Paired-pulse facilitation (PPF) was calculated as the amplitude of the second response divided by that of the first and was used for comparison with previous studies of cerebellar plasticity (Salin et al. 1996). Data from individual slices were from a single presentation of the stimulus protocol, except in five slices, in which data were an average of two presentations with ≥30 min between. All data are reported as mean ± SE in either absolute or normalized units (unless otherwise noted). Statistical comparisons among data were performed using an ANOVA or a paired t-test.

The stimulation methods we use can sometimes be associated with changes in the recruitment of the stimulated fibers, reflected in changes in the presynaptic fiber volley (Salin et al. 1996). In some of our experiments, the fiber volley was difficult to distinguish from the stimulus artifact, but we were able to do so in nine separate experiments. In these cases, the peak negativity associated with the fiber volley was slightly decreased in the 2- to 5-min posttrain period (normalized to pretrain value, 0.91 ± 0.048, P = 0.01), but in no cases did we observe evidence of an increased fiber volley. In rat cerebellar studies, there is also an initial decrease in the fiber volley immediately following the stimulus period, followed by a slight increase (Salin et al. 1996).

Model description

We have previously described ELL parallel fiber short-term plasticity on time scales of less than a second using the so-called FD formalism (Dayan and Abbott 2001; Lewis and Maler 2002). In an FD model, a stimulus-evoked postsynaptic potential (PSP) is described by a combination of facilitation-like processes (F) and depression-like processes (D) that increase or decrease, respectively, with the PSP amplitude relative to the control amplitude (A₀). This general formalism has been used to describe many different synapses with the details of implementation varying among these cases (see references in Lewis and Maler 2002; Zucker and Regehr 2002). Our original model was based on a previous FD model of a cerebellar parallel fiber synapse (Dittman et al. 2000) to which we added a depression-like term describing disynaptic inhibition. This inhibition, which is due to parallel fiber activation of interneurons in the ELL molecular layer, is activated at mean stimulation frequencies >16 Hz; this is true for both fixed-interval and random-interval stimulation (Lewis and Maler 2002), suggesting that a sequence of multiple high-frequency events is required to recruit inhibition. In this paper, we present a slightly simplified version of our original model (Lewis and Maler 2002) to facilitate our analyses. First, because we limit our stimulation frequency to a mean of 16 Hz, we can discount the inhibitory process. Second, the F process in the original model contained a nonlinear squashing function (as in Dittman et al. 2000; see Eq. 3 in Lewis and Maler 2002) so that F would not increase beyond a value of 1. Here, we eliminate this nonlinearity because the squashing function is nearly linear for the relatively low stimulation frequencies considered. Our reduced model is summarized in the next set of equations (Eqs. 1–3).

\[ \text{PSP}_i = A_0 \times F(t) \times D(t) \] (1)
\[ \frac{dF(t)}{dt} = \frac{F_0 - F(t)}{F(t) + \Delta_F} \quad \text{and} \quad F(t) \to F(t) + \Delta_F \quad \text{when} \quad t = t_i \] (2)
\[ \frac{dD(t)}{dt} = \frac{1 - D(t)}{\tau_D} \quad \text{and} \quad D(t) \to D(t) - D(t) D(t) \quad \text{when} \quad t = t_i \] (3)

The response of the model to the \( i \)th stimulus delivered at a time \( t_i \) (in s) is given by Eq. 1, with the dynamics of facilitation and depression given by Eqs. 2 and 3, respectively. At each stimulus time \( t_i \), the value of \( F \) is increased by the update magnitude \( \Delta_F \) and then recovers exponentially to its resting value \( F_0 \) with a time constant \( \tau_F \). Similarly, at each stimulus, \( D \) is decreased by an amount given by the product \( FD \) and recovers exponentially to a value of 1 with a time constant \( \tau_D \). Both \( F \) and \( D \) terms can be associated with the calcium-dependent vesicle release process, with the product \( FD \) indicating transmitter release probability and \( F_0 \) as the baseline release probability (Dittman et al. 2000).

In summary, the present model has five parameters (\( A_0, F_0, \Delta_F, \tau_F, \tau_D \), and \( \tau_P \)). The parameter \( \tau_P \) is fixed to 0.083 s, as in our previous study (Lewis and Maler 2002); \( A_0 \) is a constant scaling factor set to \( 1/F_0 \) when we consider normalized responses. The remaining parameters \( (F_0, \Delta_F, \tau_F, \text{and} \tau_D) \) are considered free parameters and will be addressed individually under RESULTS.

Model simulations

In Figs. 4 and 5, we show results from model simulations, using different simulation frequencies and different values of the parameter \( F_0 \) in each simulation. We delivered random Poisson trains (stimulus intervals \( t_i \) that are exponentially distributed as in the experiments) consisting of 1000 pulses to our model at mean frequencies from 1 to 50 Hz. For each mean frequency, we computed the steady-state...
response over the train in terms of the mean normalized PSP size given by the model (Eq. 1 with \( A_0 = 1/F_0 \)). In general, there was a particular frequency for which the response was maximal (see dotted lines in Fig. 5A; this was designated as the preferred frequency and is the quantity plotted in Fig. 5B as a function of \( F_0 \). We also calculated the SD and coefficient of variation (CV = SD/mean) of these responses for one stimulation frequency (16 Hz) to provide the predictions shown in Fig. 4B.

**RESULTS**

**Long-term enhancement at the parallel fiber synapse**

The goal of the present study was to characterize the changes in short-term synaptic plasticity (time scales of tens of milliseconds) during the development of synaptic changes on much longer time scales (minutes). We first describe a LTE produced by patterned stimulation of ELL parallel fibers that is similar to the presynaptic LTP expressed by parallel fibers in the rat cerebellum (Castillo et al. 2002; Chen and Regehr 1997; Jacoby et al. 2001; Salin et al. 1996).

To induce LTE, we used a stimulus protocol lasting slightly <90 s and consisting of five repetitions of a 200-\( \mu \)s 16-Hz Poisson train with 5 s between each train (5-train protocol, see METHODS). This protocol resulted in an enhancement of the field potential excitatory postsynaptic potential (fEPSP) amplitude by about 30% (\( n = 12 \) slices; Fig. 1A). We monitored this enhancement at regular intervals for 5 min after train stimulation. LTE lasted about 25 min, at which time the normalized fEPSP was 1.06 ± 0.054 and not significantly different from control (\( P = 0.34 \)), but we did not systematically track the entire time course of recovery. We refer to this phenomenon as a LTE. PPF was variable, but in parallel with the LTE, there was a significant decrease (15%; \( P = 0.02; n = 12 \) slices) in PPF in the postrain period (2–5 min): PPF was 2.06 ± 0.13 in the pretrain control period and 1.78 ± 0.078 in the postrain period. At 25 min postrain, PPF increased to 1.87 ± 0.17 and was not significantly different from pretrain controls (\( P = 0.30 \)). LTE did not occur with a single repetition of the 16-Hz Poisson train (\( n = 8 \) slices; Fig. 1A); during the postrain period following a single train (2–5 min) the fEPSP amplitudes, as well as PPF (2.07 ± 0.15), were not significantly different from control (\( P = 0.80 \) and \( P = 0.31 \), respectively).

To test whether the LTE we observed in the ELL was similar to the presynaptic LTP observed in rat cerebellar slices (Salin et al. 1996), we applied the adenylate cyclase activator forskolin (10 \( \mu \)M) to the bath. Forskolin induced an enhancement (+50%) similar to that described in rat cerebellar slices (\( n = 5 \) slices). The mean normalized fEPSP increased after forskolin treatment to 1.53 ± 0.13 (\( P = 0.001 \)) compared with control) while PPF decreased to 1.6 ± 0.13 (\( P = 0.03 \)). The 5-train protocol delivered during the forskolin-induced enhancement did not produce further enhancement of the normalized fEPSP amplitude (Fig. 1B; \( P = 0.47 \) compared with pretrain) nor did it change PPF (1.50 ± 0.14; \( P = 0.15 \)). Pretreatment with forskolin therefore occludes the train-induced LTE that we observe in ELL. Further, there was no significant LTE when we repeated the 5-train protocol in the presence of the PKA inhibitor H-89 (0.2 \( \mu \)M; \( n = 3 \)); under these conditions there was a slight but insignificant enhancement (\( P = 0.07 \); normalized postrain fEPSP amplitude of 1.183 ± 0.021). Overall, these data suggest that the LTE is mediated by a presynaptic cAMP/PKA-dependent signaling pathway that is biochemically similar to the previously described cerebellar LTP.

A number of overlapping processes are thought to be involved in long-term plasticity at the ELL parallel fiber synapse (Bastian 1999; Han et al. 2000), among them a postsynaptic N-methyl-D-aspartate (NMDA)-dependent long-term depression (LTD). To determine if this LTD was activated by our stimulus protocol and was thus actively offsetting the expression of LTE, we repeated the 5-train protocol in the presence of the NMDA antagonist 2-amino-5-phosphonovaleric acid (APV; 50 \( \mu \)M). With APV, there was a significant increase in the level of LTE, as compared with that observed under control conditions, only during the first minute of the postrain period (\( n = 5 \); \( P = 0.03 \)) (see Fig. 1, open symbols). Later in the postrain period (2–5 min), the increase in the level of LTE became insignificant (\( P = 0.18 \)). In contrast, during the entire postrain period, PPF was not significantly different between control and APV conditions (1 min postrain, \( P = 0.7 \); 2–5 min postrain, \( P = 0.6 \)). These observations suggest that the transient depression evident in the 1-train and forskolin conditions (Fig. 1) may be postsynaptically mediated and NMDA dependent. Thus this depression could be acting to control the expression of the LTE we have described (we did not pursue this possibility further in the current study).

**Short-term synaptic dynamics during LTE induction**

Because our stimulation protocol consisted of multiple repeats of a single Poisson train, we were able to efficiently assess the short-term dynamics of this synapse over a range of frequencies. This marks an improvement over previous studies of long-term plasticity, using paired-pulse protocols and fixed-interval trains that involve only one interstimulus interval, and thus sample the synaptic dynamics at only one frequency. Here, we considered the responses to the first 32 stimuli of each random train and used our model to quantify the changes.
in these dynamics during the onset of LTE. We limited our analysis to this brief subset of responses to preclude significant influences of long-term processes; because long-term plasticity involves slow time scales, their influence changes relatively little over the time scales that short-term processes act. Further, the 5 s between successive trains allowed any short-term dynamics (time constants less than 1 s) to recover. In addition to our pharmacological comparison with presynaptic LTP in rat cerebellum (Salin et al. 1996), we present here a novel method of testing whether the changes in synaptic dynamics during the onset of LTE in ELL could also be explained by changes in the baseline probability of release. Baseline probability of release is directly, and uniquely, related to the parameter \( F_0 \) in our model (Dittman et al. 2000) and thus was expected to increase during LTE.

Our model involves three free parameters \( (F_0, \Delta_F, \text{ and } \tau_F) \). So to test the impact of varying \( F_0 \) alone, we first fit the model to the mean responses \( (n = 12) \) over the first 32 stimuli of the first train in the 5-train protocol \( (F_0 = 0.10; \Delta_F = 0.23; \tau_F = 0.079 \text{ s}; 10.4\% \text{ error; Fig. 2, top}) \). The parameters \( \Delta_F \) and \( \tau_F \) then were held constant at these values, with \( F_0 \) as the only free parameter. Figure 2 shows the mean response data (normalized to the first response of the first train) over the first 2 s of stimulation in the 1st, 3rd, and 5th trains, along with the model fits (and corresponding estimates of \( F_0 \)). With \( F_0 \) as the only free parameter, the model accurately fit the mean data for each of the five trains, as indicated by the small fitting errors (Fig. 2).

3B, open circles). In particular, the model captures two prominent aspects of the data: the decrease in response variance over successive trains and the decrease in peak response. We emphasize that the pattern of stimulation in each train is identical, so that the differences observed over the trains (other than those due to random variations) are due to longer-term changes in the dynamics of the parallel fiber synapse. Performing a similar analyses with either \( \Delta_F \) or \( \tau_F \) as the free parameters (and the other two parameters held constant) resulted in much higher fitting errors (Fig. 3B), whereas leaving all three parameters free to vary led to only a marginal decrease in the fitting error compared with varying \( F_0 \) alone (Fig. 3B, closed squares). This suggests that the changing synaptic dynamics over our stimulation protocol can be explained largely by changes in the parameter \( F_0 \), suggesting that the transmitter release probability is increasing during the onset of the LTE.

Thus far we have considered data that was averaged over many experiments. To further test the model, we performed the fitting analysis (as above) using the data from individual experiments. Figure 3A (open circles) shows the average value of \( F_0 \) found for each of the slices during each of the 5 consecutive trains. As with the mean data, the values of \( F_0 \) increased significantly over the course of the trains \( (P = 0.03) \), and further, when the value of \( F_0 \) found for the 5th train was between 0.1 and 0.2 (9/12 cases), this value was correlated with the level of LTE measured in the 2- to 5-min posttrain period \( (R = 0.82, P = 0.006) \).

In the previous section, we suggested that treating slices with FSK occludes the train-induced LTE by increasing the probability of transmitter release via a similar mechanism. This provides a specific prediction about how the parameter \( F_0 \) should vary during train stimulation in the presence of FSK. First, the value of \( F_0 \) should be greater than control during the 1st train. Second, if the LTE is occluded by FSK and not simply masked, then \( F_0 \) should not change during the 5-train protocol. This is exactly what we observed (Fig. 3A, closed squares).

As mentioned previously, response variability decreases over the course of the 5 random trains (Fig. 2). To quantify this behavior we calculated the SDs of the responses over the first 2 s of stimulation for each of the 5 trains. We used the mean

![FIG. 3. Summary of changes in \( F_0 \) during the induction of LTE. A: mean ± SE values of \( F_0 \) found from the model fits to data from individual experiments under control conditions (open circles; \( n = 12 \)) and those during bath application of 10 \( \mu \text{M} \) FSK (closed circles; \( n = 5 \)) plotted as a function of train number during repeated train stimulation. B: root-mean-squared errors for fits to mean responses from the control experiments under 4 different fitting conditions: only \( F_0 \) was free to vary \( (\Delta_F = 0.23; \sigma_F = 0.079 \text{; open circles}); only \Delta_F \) was free to vary \( (F_0 = 0.10; \sigma_F = 0.079 \text{; closed inverted triangles}); only \( \tau_F \) was free to vary \( (F_0 = 0.10; \Delta_F = 0.23 \text{; closed triangles}); and all three parameters \( (F_0, \Delta_F, \text{ and } \tau_F) \) were free to vary (closed squares).](https://www.jn.org)
response data so that any fluctuations due to noise (i.e., not due to the dynamics per se) would be averaged out. Under control conditions, there is a clear decrease in SD during the 5-train protocol, whereas during FSK treatment, the SD is lower and does not show a trend with train number (Fig. 4A). This result parallels that shown in Fig. 3A and is due mainly to the changing release probability (model parameter $F_0$). This is illustrated by plotting the SD as a function of the value of $F_0$ found for the corresponding train (Fig. 4B; open circles, control; open squares, FSK). The solid line in Fig. 4B shows the SD of the model responses 16-Hz random stimulation over the same range of $F_0$. The data for both control and FSK conditions clearly follow the model predictions, suggesting that a main determinant of response variability under these conditions is the baseline release probability. Also shown in Fig. 4B is a similar relationship for the CV, verifying that there are no major effects due to a change in mean response amplitude.

Taken all together, our results show that the dynamics of the parallel fiber synapse in ELL during LTE onset can be accounted for by changes in the parameter $F_0$ alone, illustrating in a novel way that the observed LTE is attributable to factors influencing the baseline probability of transmitter release.

**Frequency dependence of short-term synaptic dynamics**

We developed our model under simplifying conditions to facilitate our analysis. Nonetheless, we can probe the simplified model under more general conditions to gain insight into the functional implications of changing baseline release probability (Dittman et al. 2000), for example, via mechanisms such as the LTE we describe in this study.

In a set of simulations, we delivered random Poisson trains (1000 pulses) to our model using mean frequencies from 1 to 50 Hz. For each frequency of random stimulation and choice of value for $F_0$, the mean normalized PSP size ($Eqs. 1$; $A_0 = 1/F_0$) over the stimulation period was calculated, thus providing the frequency response for the model. Figure 5A shows the results for two different values of $F_0$ (0.1 and 0.2). Similar to what we have previously described for the more complicated model (Lewis and Maler 2002), the present model exhibits a band-pass behavior; the PSP size is maximal for a particular mean frequency of stimulation, preferred frequency (dotted vertical lines in Fig. 5A). Interestingly, this preferred frequency decreases with increasing values of the parameter $F_0$ in an almost linear manner (Fig. 5B). The details of this behavior will depend on the parameters associated with both $F$ and $D$, but we have used the parameter values that best fit our data. The CV of the responses at this preferred frequency decreases in a similar way with $F_0$ (not shown, but see Fig. 4B for 16-Hz stimulation), suggesting that a number of synaptic filtering properties can be influenced and controlled by processes such as the LTE we describe in this paper. In this way, long-term synaptic enhancement can be thought of, not only as a mechanism for memory storage, but also as a means for changing synaptic filtering on much shorter time scales.

**DISCUSSION**

Long-term synaptic changes are widely accepted as a substrate for learning and memory. Such changes in the efficacy of a synapse are widely observed, yet vary considerably in their magnitude and time course. Further, many synapses that exhibit plasticity on long time scales (minutes to hours) are also influenced by dynamics on much shorter time scales (milliseconds and seconds). Detailed descriptions of how these synaptic processes interact on varying time scales will be essential for understanding the dynamics of information processing and storage in the nervous system.

We have demonstrated in this paper that the parallel fiber feedback pathway to the ELL of an electric fish exhibits a LTE that is similar to the presynaptic LTP observed in rat cerebellum (Salin et al. 1996). Further, we have presented evidence that, during the induction of LTE, there is a progressive increase in the probability of transmitter release at these ELL synapses. In addition, our study builds on previous work in two important ways.

First, we provided an accurate characterization of short-term dynamics at the parallel fiber synapse over a range of frequen-

![FIG. 4. Response variability due to short-term dynamics. A: SD of the mean response data (see Fig. 2) as a function of train number for both control (open circles) and during FSK treatment (open squares). B: SD and the coefficient of variation (CV) plotted as a function of the parameter $F_0$ found for each train. Data are shown for both control (SD, open circles; CV, closed circles) and FSK (SD, open squares; CV, closed squares) conditions. Also shown are the model predictions (solid lines) from 16 Hz random stimulation for both SD and CV over the same range of $F_0$ (parameters other than $F_0$ have the same values as those reported in Fig. 2).](jneurosci.org)
cies. Our methods follow from work in other systems that have used Poisson trains to characterize short-term synaptic dynamics (Markram and Tsodyks 1996; Varela et al. 1997). However, previous work on long-term enhancement of the parallel fiber synapse in mammalian cerebellum has involved fixed-interval trains and paired-pulse stimulation protocols, which sample only a single frequency at a time (Salin et al. 1996). While these studies have also linked changes in release probability to LTE at the parallel fiber synapse, none have used methods that quantified the dependence of these changes over a range of frequencies.

Second, we have characterized the evolution of short-term synaptic dynamics during the induction of LTE and not simply after its expression. This is an important distinction because, under normal physiological conditions, there is likely a dynamic balance between many different types of plasticity. In such situations, an understanding of the slow changes in synaptic plasticity will be critical. A few previous studies of other synapses have monitored short-term synaptic dynamics before and after the induction of long-term synaptic plasticity (Finnerty and Connors 2000; Finnerty et al. 1999; Markram and Tsodyks 1996; Toth et al. 2000). In the cases in which changes in short-term dynamics were observed, they were also consistent with a change in the baseline probability of transmitter release (Finnerty et al. 1999; Markram and Tsodyks 1996; Toth et al. 2000). However, because of the methods used, none of these studies were able to monitor synaptic dynamics while the long-term plasticity was developing.

Under natural circumstances, the parallel fiber synapses in ELL will be influenced by a number of dynamic processes (expressed both pre- and postsynaptically), overlapping on a variety of time scales. For simplicity, we have limited our studies to two specific forms of presynaptic plasticity: short-term plasticity (facilitation and depression) with a time scale near 100 ms and a LTE with a time scale around 20 min. There are no guarantees that postsynaptic changes are not influencing our results. However, it is generally accepted that the parallel fiber LTP in mammalian cerebellum is presynaptically mediated. It is likely, by analogy, that the LTE we describe is presynaptic as well. More important though is that long-term postsynaptic changes would have to affect short-term dynamics in a manner that is very similar to those resulting from changes in baseline release probability. The fact that our model, based on short-term facilitation and depression, can explain the changes in dynamics during LTE is further evidence for a presynaptic locus. Postsynaptic modifications (e.g., changes in receptor desensitization) may influence short-term dynamics (Zucker and Regehr 2002), but long-term postsynaptic changes are usually associated with processes that change the gain of the synapse without affecting the short-term dynamics.

In the least, our stimulation protocol does recruit a depression-like process with a time scale of a few minutes (Fig. 1), but we do not yet know its underlying mechanism. It may be related to the postsynaptic NMDA-dependent LTD expressed at this synapse (Bastian 1998); our stimulation protocol is much different in pattern, frequency, and duration from that used by Bastian (1998), so we may be observing a partial activation of this LTD. Nonetheless, such an LTD could be acting to offset the LTE we observe so that the synaptic gain is tightly regulated. In this way, the dynamics (in terms of short-term filtering) could be regulated by LTE independent of any net change in synaptic gain.

Another process contributing to the dynamics at the ELL parallel fiber synapse, although not directly related to synaptic plasticity, is inhibition. We have previously described this disynaptic inhibition (Lewis and Maler 2002), but for simplicity we have purposely chosen a stimulation protocol in the present study that minimizes its influence. However, under natural conditions, this inhibition will certainly lead to more diverse dynamics, by controlling both synaptic gain and filtering properties.

In general, the functional implications of long-term changes in release probability on short-term synaptic dynamics are not known but have been extensively hypothesized (Tsodyks and Markram 1997). Short-term plasticity confers specific filtering properties to a synapse (Fortune and Rose 2001), and thus changing these dynamics through long-term plasticity will lead to different filtering properties (Fig. 5) (Abbott et al. 1997; Buonomano 2000; Tsodyks and Markram 1997). Some forms of long-term plasticity may then provide a means of controlling both gain and frequency selectivity of a neuronal pathway. In this context, the ELL parallel fiber system of the weakly electric fish provides an ideal opportunity to test these hypotheses. These synapses exhibit long-term changes that are involved in sensory processing on time scales greater than tens of minutes (Bastian 1998; Han et al. 2000), and yet they also exhibit short-term dynamics (time scales of seconds) that are particularly relevant for prey detection (Lewis and Maler 2002; Maclver et al. 2001). Because of their proximity to the sensory periphery, as well as their strong link to a functional context, these synapses provide an excellent system by which to study the role of synaptic plasticity on multiple time scales in adaptive sensory processing (Bastian 1999; Bell 2001).

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