Modulation of Calcium-Dependent Postsynaptic Depression Contributes to an Adaptive Sensory Filter

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Bastian, Joseph. Modulation of calcium-dependent postsynaptic depression contributes to an adaptive sensory filter. J. Neurophysiol. 80: 3352–3355, 1998. The ability of organisms to ignore unimportant patterns of sensory input may be as critical as the ability to attend to those that are behaviorally relevant. Mechanisms used to reject irrelevant inputs range from peripheral filters, which allow only restricted portions of the spectrum of possible inputs to pass, to higher-level processes, which actively select stimuli to be “attended to.” Recent studies of several lower vertebrates demonstrate the presence of adaptive sensory filters, which “learn,” with a time course of a few minutes, to cancel predictable patterns of sensory input without compromising responses to novel stimuli. Predictable stimuli include “reafferent” stimuli, which occur as a result of an animal’s own activity, as well as stimuli that are simply repetitive. The adaptive characteristic of these filters depends on an anti-Hebbian form of synaptic plasticity that modulates the strength of multisensory dendritic inputs resulting in the genesis of “negative image” signals, which cancel the predicted pattern of sensory afference. This report provides evidence that the mechanism underlying the anti-Hebbian plasticity involves the modulation of a calcium-dependent form of postsynaptic depression.

INTRODUCTION

Sensory inputs generated as a consequence of an animal’s activity as well as other repetitive stimuli may not carry useful information; instead, such stimuli are potentially disruptive and may mask behaviorally relevant signals. Studies of several lower vertebrates demonstrated an adaptive filtering mechanism, within the earliest stages of electrosensory and lateral line systems, which enable single cells to preferentially attenuate predictable inputs (Bell et al. 1997). A surprisingly simple mechanism, involving an anti-Hebbian form of synaptic plasticity in which correlated pre- and postsynaptic activity results in reduced rather than increased excitatory synaptic strength, forms the basis for the filter, and the similarities of the mechanism among the species studied thus far suggest that these filters may be common features of vertebrate sensory systems (Bastian 1995; Bell et al. 1993; Montgomery and Bodznick 1994).

The weakly electric fish Apterontus leptorhynchus, used in this study, generates an electric field around its body with an electric organ located in the trunk and tail. Electrosensors scattered over the body surface monitor the amplitude and phase of this field and encode field changes caused by the presence of objects near the fish (electrolocation) as well as changes caused by signals generated by other electric fish (electrocommunication) (Bullock and Heiligenberg 1986). Electoreceptors are also sensitive to changes in posture because movements of the trunk and tail alter the position of the electric organ and therefore the relative field strength at different regions of the body. Although electoreceptors respond strongly to these movement-related or reaferent stimuli, second-order cells respond weakly, if at all (Bastian 1995).

The general features of the adaptive filtering mechanism are well understood. Figure 1 illustrates the mechanism and the relevant circuitry of gymnotid weakly electric fish. Electrosensory afferents terminate within a medullary nucleus, the electrosensory lateral line lobe (ELL), providing input to basilar dendrites of pyramidal cells that project to higher-order processing stations. The ELL has a cerebellar-like organization characterized by a thick molecular layer composed of parallel fibers (dorsal molecular layer, DML) and other axons (ventral molecular layer, VML) that convey information from multiple sensory modalities to the apical dendrites of pyramidal cells and ELL inhibitory interneurons (Maler et al. 1981). Predictable stimuli, reaferent input of Fig. 1, are canceled by the integration of “negative image” inputs received at the cell’s apical dendrites. Negative image inputs include descending electrosensory and proprioceptive information and possibly corollary discharges of motor commands (Sas and Maler 1987). Plasticity at the apical dendritic synapses, governed by an anti-Hebbian rule (Bell et al. 1993; Montgomery and Bodznick 1994), gives rise to the adaptive nature of the filter, allowing the system to learn to cancel changing patterns of input. According to this rule, repetitive occurrence of increased receptor afferent input (pyramidal cell depolarization) reduces the strength of concomitantly active excitatory dendritic inputs and may also potentiate inhibitory inputs. Thus the net synaptic input to the apical dendrites can be converted from excitation to inhibition, thereby canceling increased excitation received from the periphery. Potentiation of apical dendritic excitatory postsynaptic potentials (EPSPs) and possibly depression of inhibitory postsynaptic potentials (IPSPs) occurs given repetitive pyramidal cell hyperpolarization allowing the system to also cancel stimuli that reduce pyramidal cell firing (Bastian 1996a,b). The experiments of this study tested the recently proposed hypothesis that Ca$^{2+}$-dependent postsynaptic depression contributes to the plasticity at pyramidal cell dendritic synapses (Bastian 1998).
Recording and stimulation

by the DML tetanus alone (Fig. 2 containing action potentials were excluded from the analysis; most shading) as was the plasticity that normally develops evoked EPSPs from initiating action potentials. EPSP amplitudes again presented alone, and the test EPSP amplitudes reverted remain stable with this test-pulse protocol (Bastian 1998). toward values seen before the paired stimulation (Fig. 2,

nA) postsynaptic hyperpolarization to prevent the DML or VML-stage of these experiments the DML or VML tetanus was old; hence, test stimuli were presented along with a small (0.3 EPSPs, respectively (Sandkuhler et al. 1997). Electrodes were beveled iontophoretically injected via hyperpolarizing current injection (4 the last 30 s of the tetanus-alone period (Fig. 2). Results of these experiments showed that the DML tetanus depressed test EPSPs to 64.8 ± 3.3% of their control amplitudes (P < 0.0001, n = 40, t-test), whereas the VML tetanus increased test EPSPs to 183.4 ± 7.5% of the control value (P < 0.0001, n = 40, t-test).

After 2 min of tetanic stimulation, plasticity was induced by pairing the tetanus with 100 ms (0.8 nA) postsynaptic hyperpolarization or depolarization. The paired hyperpolarization partially reversed the test EPSP depression caused by the DML tetanus alone (Fig. 2A, leftmost shaded region); however, tetani applied to the VML had the opposite effect (Fig. 2B, leftmost shaded region). Comparison of EPSPs averaged over the 30-s control period with those from the last 30 s of the tetanic stimulation showed that the DML tetanus depressed test EPSPs to 64.8 ± 3.3% of their control amplitudes (P < 0.0001, n = 40, t-test), whereas the VML tetanus increased test EPSPs to 183.4 ± 7.5% of the control value (P < 0.0001, n = 40, t-test).

Data analysis

Intracellular recordings were made with thin-wall aluminosilicate sharp micropipettes filled with either 3 M K-acetate (normal-cell recording) or with 3 M K-acetate plus 100 mM 1,2-bis(2-aminophenoxy)ethane-N,N',N''-tetraacetic acid (BAPTA-loaded cells) (Sandkuhler et al. 1997). Electrodes were beveled to final impedances ranging from 100 to 150 MΩ. BAPTA was iontophoretically injected via hyperpolarizing current injection (4 Hz negatively offset sine wave, 0.5 nA peak to peak for 5 min or −0.5 nA DC for 3 min).

DML and VML fibers were electrically stimulated via bipolar stainless steel wire electrodes insulated to the tip. Monopolar 0.2-ms stimulus pulses of amplitudes ranging from 10 to 50 μA were used, and electrode placement in the appropriate pathways was verified by recording characteristic evoked potentials (Bastian 1998). Pyramidal cell resting potentials are quite close to threshold; hence, test stimuli were presented along with a small (0.3 nA) postsynaptic hyperpolarization to prevent the DML or VML-evoked EPSPs from initiating action potentials. EPSP amplitudes remain stable with this test-pulse protocol (Bastian 1998).

RESULTS

In vivo studies have shown that two separate pathways, the ELL dorsal and ventral molecular layers (Fig. 1, DML and VML, respectively) can contribute to the negative image inputs in Apteronotus (Bastian 1996a,b, 1998). Also, the anti-Hebbian plasticity that normally shapes the negative image inputs can be induced by pairing tetanic DML or VML stimulation with pyramidal cell hyper- or depolarization. Figure 2, A and B, summarizes the effects of DML or VML tetanic stimulation alone and tetani paired with postsynaptic current injection on the sizes of pyramidal cell EPSPs evoked by individual test stimuli. Initially, test stimuli were presented alone to either pathway at 1/s for 30 s to assess baseline EPSP amplitudes. After this, each test stimulus was preceded by a 100-ms tetanus (15-ms interpulse interval); the DML tetanus depressed subsequent DML test EPSPs (Fig. 2A, leftmost shaded region); however, tetani applied to the VML had the opposite effect (Fig. 2B, leftmost shaded region). Comparison of EPSPs averaged over the 30-s control period with those from the last 30 s of the tetanic stimulation showed that the DML tetanus depressed test EPSPs to 64.8 ± 3.3% of their control amplitudes (P < 0.0001, n = 40, t-test), whereas the VML tetanus increased test EPSPs to 183.4 ± 7.5% of the control value (P < 0.0001, n = 40, t-test).

After 2 min of tetanic stimulation, plasticity was induced by pairing the tetanus with 100 ms (0.8 nA) postsynaptic hyperpolarization or depolarization. The paired hyperpolarization partially reversed the test EPSP depression caused by the DML tetanus alone (Fig. 2A, heavy shading, open circles) and VML tetanus plus hyperpolarization resulted in additional test EPSP potentiation (Fig. 2B, heavy shading, open circles). The DML and VML test EPSP amplitudes, averaged over the last 10 s of the tetanus plus hyperpolarization periods, increased by 28.7 ± 5.7 and 19.3 ± 3.6% for DML and VML test EPSPs, respectively (P = 0.0001, t-tests). During the final stage of these experiments the DML or VML tetanus was again presented alone, and the test EPSP amplitudes reverted toward values seen before the paired stimulation (Fig. 2, A and B, rightmost shading).

The idea that calcium-dependent postsynaptic depression contributes to the anti-Hebbian plasticity was tested by repeating the experiments of Fig. 2, A and B, with pyramidal cells loaded with the rapid calcium chelator BAPTA. The initial depression of DML-evoked test EPSPs caused by the tetanus alone was blocked by this treatment (Fig. 2C, leftmost shading) as was the plasticity that normally develops
when tetanus is paired with postsynaptic hyper- and depolarization (Fig. 2C, heavy shading). BAPTA treatment also altered the responses to VML tetanus alone (Fig. 2D, leftmost shading), increasing the potentiation from an average of 183.4 ± 7.5% in normal cells to 241.0 ± 12.8% (P = 0.0004, t-test). Additionally, as in the case of the DML, BAPTA treatment reduced the plasticity normally induced by VML tetanus coincident with postsynaptic hyper- or depolarization (Fig. 2D, heavy shading). The potentiation seen after paired hyperpolarization in normal cells was completely eliminated, and the depression normally seen after paired depolarization was reduced. However, a statistically significant residual depression was still seen after BAPTA treatment (see legend of Fig. 2).

BAPTA treatment did not significantly effect control EPSP amplitudes. Baseline DML-evoked EPSPs recorded in normal and BAPTA-treated cells averaged 3.58 ± 0.33 and 3.64 ± 0.43 mV, respectively (P = 0.92, t-test n = 40 and 29). Control VML-evoked EPSPs averaged 1.58 ± 0.12 and 1.66 ± 0.1 mV in normal and BAPTA-treated cells, respectively (P = 0.59, t-test, n = 40 and 23).

**Discussion**

It was recently proposed that the opposite effects of DML and VML tetanus alone as well as the similar patterns of plasticity induced by tetani paired with postsynaptic hyper- or depolarization might result from the interplay of postsynaptic depression and pathway-specific patterns of presynaptic potentiation (Bastian 1998). It is known that the DML parallel fibers display posttetanic potentiation (PTP) in vitro (Wang and Maler 1998), and it was proposed that tetanic DML stimulation in vivo also causes a calcium-dependent postsynaptic depression to develop that outweighs the PTP. Hence, with tetanus alone, the DML-evoked EPSPs depress, while the tetanus-induced depression (Fig. 2A, heavy shading) was completely eliminated, and the depression normally seen after paired depolarization was reduced. However, a statistically significant residual depression was still seen after BAPTA treatment (see legend of Fig. 2).

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The VML input to pyramidal cells is known to express PTP having different properties compared with that of the DML (Wang and Maler 1998), and it was proposed that normally the VML PTP outweighs the concurrently induced...
postsynaptic depression, resulting in a net increase in EPSP amplitude caused by tetanus alone. Postsynaptic hyper- and depolarization then modulates the postsynaptic depression, resulting in plasticity similar to that seen at the DML synapses, but the phenomenon is superimposed on net potentiation rather than depression (Fig. 2B). The increase in EPSP amplitude caused by tetanus alone in normal cells might not reflect the true extent of the VML PTP because the simultaneous build-up of postsynaptic depression should partially mask this effect. Blockade of the postsynaptic depression is therefore expected to augment the VML potentiation caused by tetanus alone as well as eliminate the anti-Hebbian plasticity. This prediction was also fulfilled in experiments with BAPTA-loaded pyramidal cells (compare Fig. 2, B and D).

That BAPTA treatment reduces the anti-Hebbian plasticity supports the hypothesis that the ability of pyramidal cells to reject predictable afferent inputs is, at least in part, due to a calcium-dependent form of postsynaptic depression. Although this study focused on EPSP plasticity, earlier studies clearly showed that putative DML- and VML-evoked IPSPs were also modulated by these stimulation protocols. Tetanic stimulation of either pathway paired with postsynaptic depolarization potentiated these IPSPs (Bastian 1996b, 1998), and, given appropriate latency and duration, modulation of IPSP amplitudes could contribute to the changes in EPSPs seen in this study. Furthermore, recent in vitro studies by Berman and Maler (1998a,b) demonstrating that stimulation of these descending pathways typically evokes tightly coupled EPSP–IPSP combinations provides additional support for this idea. Additional in vivo studies are needed to determine the degree to which DML- and VML-evoked IPSPs contribute to the rejection of reafferent stimuli and the generation of negative image inputs.

The similarity of the brain areas showing this plasticity to the cerebellum suggests that the depression may be similar to long-term depression documented for parallel fiber inputs to Purkinje cells, and, under suitable stimulus conditions, the anti-Hebbian plasticity can persist for tens of minutes (Bell et al. 1997). In normally functioning animals, however, the synaptic strengths of negative image inputs may be continuously modulated to optimize the rejection of currently predictable inputs. The anti-Hebbian plasticity allows the pyramidal cells to operate as simple negative-feedback systems in which any afferent input occurring repeatedly with simultaneously active dendritic inputs results in response cancellation. The adaptive filtering mechanism described here could be implemented in a wide variety of sensory systems contributing to an animal’s ability to ignore predictable inputs without compromising sensitivity to those carrying important information.

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