Spike-Timing-Dependent Plasticity of Inhibitory Synapses in the Entorhinal Cortex

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Haas, Julie S., Thomas Nowotny, and H.D.I. Abarbanel. Spike-timing-dependent plasticity of inhibitory synapses in the entorhinal cortex. J Neurophysiol 96: 3305–3313, 2006. First published August 23, 2006; doi:10.1152/jn.00551.2006. Actions of inhibitory interneurons organize and modulate many neuronal processes, yet the mechanisms and consequences of plasticity of inhibitory synapses remain poorly understood. We report on spike-timing-dependent plasticity of inhibitory synapses in the entorhinal cortex. After pairing presynaptic stimuli at time $t_{\text{pre}}$ with evoked postsynaptic spikes at time $t_{\text{post}}$ under pharmacological blockade of excitation we found, via whole cell recordings, an asymmetrical timing rule for plasticity of the remaining inhibitory responses. Strength of response varied as a function of the time interval $\Delta t = t_{\text{post}} - t_{\text{pre}}$, for $\Delta t > 0$ inhibitory responses potentiated, peaking at a delay of 10 ms. For $\Delta t < 0$, the synaptic coupling depressed, again with a maximal effect near 10 ms of delay. We also show that changes in synaptic strength depend on changes in intracellular calcium concentrations and demonstrate that the calcium enters the postsynaptic cell through voltage-gated channels. Using network models, we demonstrate how this novel form of plasticity can sculpt network behavior efficiently and with remarkable flexibility.

INTRODUCTION

Experience-dependent forms of synaptic plasticity have been measured in many areas and for many types of synapses in the brain (Bliss and Collingridge 1993; Malenka and Bear 2004) and are widely thought to form the cellular basis of learning and memory. One form of plasticity induction uses tightly controlled precise temporal relationships between presynaptic and postsynaptic activations. The resulting long-lasting change in synaptic strength or spike-timing-dependent plasticity (STDP) is then expressed as a function of that precise timing relationship.

Most investigations have explored STDP in excitatory synapses (Bi and Poo 1998; Dan and Poo 2004; Egger et al. 1999; Feldman 2000; Levy and Stewart 1983; Malenka and Bear 2004), though a small subset has addressed the issue of plasticity at inhibitory synapses, reviewed in Gaiarsa et al. (2002). In the neocortex, coincidence-dependent potentiation of inhibitory synapses is calcium-dependent and can be induced by trains or bursts of postsynaptic spikes paired to a single presynaptic spike (Holmgren and Zilberter 2001). In cultured hippocampal neurons and hippocampal slices, repetitive postsynaptic spikes within 20 ms in either direction of presynaptic activation of inhibitory synapses led to a symmetrical window of potentiation of inhibitory synapses, an effect that is also calcium-dependent and dependent on chloride reversal potential modulation via the K-Cl cotransporter KCC2 (Fiuemelli et al. 2005; Woodin et al. 2003). In immediately postnatal CA1 pyramidal cells, long depolarizing postsynaptic pulses increase both amplitude and frequency of spontaneous inhibitory events, but this effect tapered off by postnatal day 12 (Gubellini et al. 2001, 2005). Also in CA1 pyramidal cells, repetitive firing of a presynaptic interneuron decreased the probability of synaptic failures in a postsynaptic neuron (Kang et al. 1998). Finally, Huang et al. (2005) showed that presynaptic stimulation at 3 Hz combined with prolonged postsynaptic depolarization of CA1 pyramidal cells resulted in long-term potentiation of slow, metabotropic inhibitory postsynaptic currents (IPSCs), a process dependent on postsynaptic N-methyl-D-aspartate receptor (NMDA-R) activation, $\text{Ca}^{2+}$ increase, and CaMKII activity.

In the present work, we report experimental results of STDP at inhibitory synapses in the entorhinal cortex (EC). The EC serves as an anatomical signaling gateway for the hippocampus (Kloosterman et al. 2003; Witter 1993). Signals passing through layer II are transformed by both the intrinsic and synaptic dynamics of the principal excitatory stellate cells (SCs) (Alonso and Klink 1993; Haas and White 2002; Klink and Alonso 1993; White et al. 1998) and by the regional theta rhythm, a 4- to 12-Hz pattern of oscillatory behavior linked to learning and memory processes (Jensen and Lisman 2005; Kahana et al. 2001; Raghavachari et al. 2001). Layer II of the EC is thought to be more seizure-resistant than layer V through effects of inhibition (Bailey et al. 2004; Bradford 1995), and inhibition is likely to modulate the activation of SCs by incoming synaptic input as well, as in other cortical areas (Hasenstaub et al. 2005). Synaptic plasticity is largely unexplored in the EC, but a handful of groups have begun to explore long-term potentiation and depression (LTP and LTD) in this area (Cheong et al. 2001; Solger et al. 2004; Yang et al. 2004; Yun et al. 2002). Understanding how SCs process their synaptic inputs, and how processing changes with those inputs, is vital to understanding how we learn and remember information.

In this work, we demonstrate a novel form of STDP at inhibitory synapses onto SCs in the entorhinal cortex. We show that this form of plasticity is dependent on a rise in intracellular calcium levels, mediated by L-type voltage-gated channels. In addition to demonstrating STDP of inhibitory synapses, we also explore the possible consequences of the observed plas-
ticity. We construct a one-dimensional chain and a two-dimensional layer model and show that the inhibitory plasticity leads to efficient and flexible control of network activity in both cases. We hypothesize that the observed plasticity of inhibitory synapses is a mechanism to control inappropriate “run-away,” seizure-like activity. Our results provide strong evidence for the importance of inhibitory inputs in maintaining an appropriate balance of synaptic signaling in the brain.

METHODS

All experiments were conducted as approved by the UCSD IACUC. Young (14- to 21-day-old) Long-Evans rats were killed by overdose to CO₂ and decapitated. The brain was quickly removed and immersed in cold (0°C) oxygenated artificial cerebral spinal fluid [ACSF; which contained (in mM) 126 NaCl, 3 KCl, 1.25 NaH₂PO₄, 2.5 MgSO₄, 26 NaHCO₃, 10 glucose, and 2 CaCl₂, buffered to pH 7.4 with 95% O₂-5%CO₂]. Horizontal slices were prepared using a Vibratome cutter (TPS). Slices were allowed to recover for 1 h prior to recording in a holding chamber at room temperature, continuously bathed in oxygenated ACSF. Slices were transferred to an immersion chamber (RC-27L, Warner Instruments) and visualized with IR-DIC optics (Zeiss Axioskop 2FS Plus, Dage CCD100), maintained at 34°C (TC-344B, Warner). Electrodes of resistance 4–6 MΩ were pulled on a horizontal puller (Sutter Instruments) and filled with a recording solution [(in mM) 135 KGluconate, 4 KCl, 2 NaCl, 10 HEPES, 0.2 EGTA, 4 MgATP, 0.3 GTP-tris, and 10 phosphocreatine-tris]. Intra-cellular signals were amplified (Axoclamp 2B, Molecular Devices), low-pass filtered (8-pole Butterworth at 5 kHz), and digitized at 10 kHz with a DAQ card (NI PCI-6035E) controlled by lab-made software created in LabView (National Instruments). In most experiments, excitatory synaptic transmission was blocked by 6-cyano-7-nitroquinoxalene-2,3-dione (CNQX, 10 μM), and d-amino-5-phosphonovaleric acid [d(-)-APV, 50 μM], obtained from Sigma (St. Louis, MO). In some experiments, 10 mM bis-(o-aminophenoxy)-N,N,N',N'-tetraacetatic acid (BAPTA, Sigma) was added to the internal solution and 15 μM nimodipine (Tocris; from stock solution of 10 mM in DMSO) was added to the bath.

We obtained whole cell recordings from superficial EC layer II neurons. We selected SCs by their superficial-most position in layer II and oblong cell bodies as well as particular characteristics of their electrophysiologic responses to long current steps: a prominent (>30%) sag in response to both depolarizing and hyperpolarizing current injections (Alonso and Klink 1993; Haas and White 2002) as well as an early first spike in response to suprathreshold stimuli (Fig. 1A). From a total of 78 neurons, the average rest potential was −61.2 ± 4.8 mV without correction for junction potential. Neurons were recorded in current-clamp mode with no extra holding current. Presynaptic, extracellular stimulation was delivered as 1-ms, 10- to 50-μA current pulses via 125-μm concentric bipolar electrodes (FHC) in layer II, within 100–200 μm of the recording electrode. We paired synaptic responses to spikes by delivering extracellular stimulations and forcing intracellular spikes using 1-ms, 2- to 3-nA current injections through the recording electrode in current-clamp mode at fixed time delays. We used 500-ms intervals between pairings for a total of 3–5 min resulting in ~320–600 pairings. Baseline and postpairing synaptic responses were collected as sets of 30 postsynaptic responses to presynaptic stimulation collected at 0.5 Hz in 5-min intervals. Series and input resistances, and resting potentials, were monitored throughout each experiment; data from cells with variations >25% in those parameters were discarded. Off-line analysis was performed in Matlab (Mathworks). Numerical methods and modeling details are described in on-line supplemental material. Values are reported as means ± SE; statistical differences were measured with ANOVA unless indicated otherwise.

RESULTS

Bidirectional STDP of inhibitory synapses

In control solution, synaptic responses of SCs to intra-layer stimulations are a mix of excitatory and inhibitory responses (Fig. 1). The excitatory effects can be blocked by addition of the antagonists CNQX (10 μM, blocking AMPA receptors) and d(-)-APV (50 μM, blocking NMDA receptors). The inhibitory responses can be blocked by addition of bicuculline (10 μM, blocking GABAA receptors) to the bath solution. To focus on the inhibitory portion of the response, all recordings reported here were made in the presence of CNQX and d(-)-APV. In each experiment, sets of 30 baseline responses, recorded at 0.5 Hz, were monitored every 5 min over a period of 10–15 min to ensure a stable synaptic response.

We paired presynaptic stimulations with single induced postsynaptic spikes (Fig. 2, arrow), and varied the interval between those stimuli, Δt = tpost − tpre between −25 and +25 ms. Pairings were repeated at a rate of 2 Hz for 5 min. After the pairings, we monitored synaptic strength for up to an hour, recording sets of 30 postsynaptic responses at 0.5 Hz, at 5-min intervals. We quantified inhibitory postsynaptic potentials (IPSPs) by their initial slopes (the slope of a linear fit to the 1st 40% of the IPSP rise, 11.6 ± 3.5 ms), and we normalized all responses to baseline. We quantified the effective plasticity as the mean IPSP slope between 20 and 30 min after pairings, normalized to the mean of the slopes for 15 min preceding pairings. We recorded IPSPs before and after pairings from a total of 78 neurons. IPSPs had initial sizes of 1.5 ± 0.9 mV.

Examples of these results are shown in Fig. 2. In the top panels, we show the evolution of changes in IPSP initial slope after pairings with Δt > 0 (A) and Δt < 0 (B). Representative IPSPs for Δt < 0 and Δt > 0 are shown in the bottom panels.
We found that for pairings in which presynaptic stimulation preceded postsynaptic stimulation \( (\Delta t = t_{\text{post}} - t_{\text{pre}} > 0) \), IPSP initial slopes potentiated. This effect was maximal for delays close to 10 ms and appears to be a very precise effect: delays of \(<5\) or \(>20\) ms were less effective in inducing potentiation. For all pairings with \( \Delta t \) between \(+5\) and \(+15\) ms, IPSP slope was enhanced on average to 134.3 \( \pm \) 5.9\% \((n = 26, P < 0.02)\) of control values. Potentiation tended to evolve slowly in time after pairings.

We found that for pairings in which \( \Delta t = t_{\text{post}} - t_{\text{pre}} > 0 \), IPSP initial slopes were diminished. As for potentiation, this effect is also very precise in its temporal requirements: for delays \(<5\) or \(>15\) ms, no substantial effect was found. For all pairings with \( \Delta t \) between \(-15\) and \(-5\) ms, IPSP slope was diminished on average to 83.2 \( \pm \) 5.8\% \((n = 19, P < 0.05)\) of control values. In contrast to potentiation, depression was usually much faster and was usually expressed immediately following pairings.

In contrast to STDP of excitatory synapses, for \( \Delta t \) near zero, we observed very little change in synaptic strength. For all pairings with \( \Delta t \) between \(-5\) and \(+5\) ms, IPSPs were on average 103.6 \( \pm \) 3.3\% \((n = 11, P > 0.3)\) of control values. Neither presynaptic stimulation alone nor postsynaptic spiking alone affected synaptic response at our stimulation rates. As an experimental control, we delivered isolated pre- or postsynaptic stimulation at the same interval and duration as in pairing experiments; IPSPs were not significantly different after pairings in both of these cases \((n = 4, P > 0.2)\).

In Fig. 3A we show a summary plot of normalized change in IPSP slope as a function of the pairing interval \( \Delta t \). For both \( \Delta t < 0 \) and \( \Delta t > 0 \), significant changes in IPSPs were maximal near \( |\Delta t| = 10\) ms and were restricted to relatively narrow temporal windows. The general trends (potentiation, depression, and temporal windows) do not depend on the details of evaluation; using IPSP slope, integral, or amplitude to evaluate the net change in synaptic strength yields the same overall effect.

Pooled time-course data are also shown in Fig. 3B and show on average that potentiation is expressed more slowly than depression. For responses that potentiated significantly \((P < 0.01)\) after pairings between \(+5\) and \(+15\) ms, the first set of IPSPs had a mean slope of 109.6 \( \pm \) 3.9\% \((n = 22)\). In comparison, the first set of IPSPs that depressed to significant levels \((P < 0.01)\) had a mean slope of 82.2 \( \pm \) 7.7\% \((n = 15)\).

**Mechanisms of inhibitory STDP**

To initiate the investigation of mechanisms for this bidirectional plasticity, we repeated the pairings at delays of \(+10\) and...
–10 ms with 10 mM BAPTA added to the intracellular medium. With intracellular calcium concentrations buffered, no significant potentiation was observed for pairings with Δt > 0 (99.5 ± 1.5%, n = 5; P > 0.7). Potentiation, but no significant depression, was observed for pairings with Δt < 0 (115.3 ± 3.3%, n = 5, P < 0.01). Results of these experiments are shown in Fig. 4 along with representative IPSPs. Our results confirm previous reports (Gaiarsa et al. 2002; Woodin et al. 2003) that plasticity of inhibitory synapses is a process dependent on intracellular calcium dynamics.

In our initial experiments, we blocked both AMPA/kainate and NMDA receptors, leaving voltage-gated calcium channels (VGCCs) as one possible site of calcium entry into the postsynaptic cell. To investigate the role of VGCCs, we repeated the pairings at delays of +10 and –10 ms with 15 μM nimodipine, to block L-type calcium channels, added to the bath solution. Under this recording condition, we saw no significant potentiation for pairings with Δt > 0 (101.89 ± 1.9%, n = 5, P > 0.4). A small but insignificant depression was observed for pairings with Δt < 0 (95.1 ± 3.9%, n = 4, P > 0.2). Results of these experiments are shown in Fig. 5 along with representative IPSPs. As an experimental control, we repeated pairings in DMSO, the solvent for nimodipine, and as in control conditions, observed depression (to 80.6 ± 4.8% of control, n = 5, P < .001) for pairings with Δt = –10. We observed potentiation for Δt > 0 (to 136.0 ± 8.3% of control, n = 3, P < 0.01).

We also recorded paired-pulse responses before and after IPSP-spike pairings to investigate possible dependence of STDP on changes in presynaptic transmission. In control conditions, inhibitory synapses onto SCs exhibit paired-pulse depression, measured as average of the second response divided by average of the first response (Kim and Alger 2001), shown in Fig. 6. Paired-pulse ratios did not depend on IPSP size for our dataset. After induction of either LTP or LTD, paired-pulse ratios were not significantly different from their prepairing values (n = 10, P > 0.4), providing one indication that presynaptic release mechanisms remain unaffected by IPSP-spike pairings.

Possible functions for inhibitory plasticity in the brain

To investigate functions of the observed plasticity rule, we first created a model of a unidirectional chain of 15 model SCs, each coupled reciprocally to a single model interneuron (Fig. 7A). A pool of background neurons, firing with sinusoidally modulated Poisson rates, provides background activity to the 15 SCs and to the interneuron. We chose initial values of excitatory couplings that would allow propagation of single spikes along the chain of SCs for most inputs. The simplicity of this chain model offers us insight into the effects of the observed inhibitory STDP rule on neuronal signal transmission.

As an output of the model, we determined the amount of inhibition necessary to terminate the propagation of spikes along the chain of SCs. We compared simulations in which the inhibitory synapses were set to a constant conductance, to simulations in which each inhibitory synapse was allowed to
change according to the plasticity rule derived from a fit to the experimental data.

For constant inhibitory synapses, two prominent changes occurred as we increased excitatory coupling between SCs along the chain in different simulations. The amount of inhibitory synaptic conductance required to terminate propagation of activity along the chain increased, and the neuron at which the propagation terminated shifted within the chain (Fig. 7C).

The second effect is due to faster response of SCs to the larger excitatory postsynaptic potentials (EPSPs), which led to faster propagation of activity along the chain. We also note that the increasing values between simulations of constant inhibitory synaptic conductance poses a serious problem for a system with excitatory plasticity: to match the growth of excitatory synaptic conductance poses a serious problem for a system requiring an artificial limit on synaptic strength.

Comparing the static and the learning cases, we note that in the homogeneous case every synapse must be strong enough to prevent spikes in the postsynaptic neuron to stop propagation; on the other hand, plasticity allows efficient tuning in which only a few synapses are needed to stop propagation. These two systems are remarkably different: the learning rule has partitioned the chain into two subchains which retain their ability to respond to other inputs, whereas the comparable homogenous system is basically unresponsive.

Another attractive feature of the observed learning rule is its flexibility: it self-adjusts the strengths of the inhibitory synapses to levels that match the amount of excitation in the network, thus solving the balance problem between excitation and inhibition presented in the preceding text. For any given amount of excitatory coupling strength (panels of Fig. 7C), static synapses required preset minimal levels of inhibition (horizontal lines in Fig. 7C), carefully tuned to each level of excitatory strength, to stop activity. In contrast, learning synapses grew autonomously according to the plasticity rule to match the required inhibition for any level of excitation (Fig. 7D).

In the simple chain, we also observed an additional critical and novel feature of inhibitory plasticity: it is self-limiting. That is, as the synaptic strength grows, it becomes increasingly likely to inhibit a requirement for induction of plasticity – the postsynaptic spike. Once that strength is achieved, its own growth signal is removed, and the synapse grows no larger according to the observed learning rule. After a learning period when that signal across the layer. In the initial state inhibition is weak and activity propagates through the whole layer, mimicking unchecked seizure-like activity (Fig. 8B). In other cases, increased inhibition resulted in a delay of the postsynaptic spike, away from the temporal window for potentiation. For these reasons, our model did not require an artificial limit on synaptic strength.

Next, we constructed a model of a cortical layer, with 400 sparsely and randomly connected excitatory SCs and 100 interneurons. The interneurons receive excitatory input from a local group of SCs, and inhibit a slightly larger local group of SCs (Fig. 8A). Again, all neurons also receive a theta-modulated Poissonian background input. We repeatedly excited three of the SCs simultaneously and observed the propagation of that signal across the layer. In the initial state inhibition is weak and activity propagates through the whole layer, mimicking unchecked seizure-like activity (Fig. 8B).

As previously, we allowed the inhibitory synapses to change according to the observed learning rule. After a learning period on the order of a few to 100 simulated seconds, we observed similar effects as in the chain model: only a few synapses potentiated, but those few synapses sufficed to efficiently control the spread of activity across the layer. The same inputs to the layer excite a well-defined small cluster of SCs, rather
than leading to uncontrolled excitation of the entire network (Fig. 8B). Again, only a small percentage of the total inhibitory synapses were required to potentiate for this effect (Fig. 8C). A few inhibitory synapses within the clusters depressed, resulting in a facilitated excitation within the cluster. Our modeling results suggest a crucial role for plasticity of inhibitory synapses in regulating neuronal transmission and control of overall network activity.

**DISCUSSION**

We have demonstrated a novel form of asymmetrical STDP in the dynamics of GABAergic synaptic couplings in the entorhinal cortex. STDP has been extensively investigated for excitatory synapses (Malenka and Bear 2004), but to our knowledge, this is the first demonstration of STDP in an inhibitory synapse in which synaptic strength is differentially strengthened or weakened by the pairing of pre- and postsynaptic activity.

A previous study of STDP of inhibitory synapses (Woodin et al. 2003) described the dependence of observed plasticity on a coincidence-dependent change in the reversal potential of the synapse, which in turn resulted from an activity-induced inhibition of the Cl⁻ cotransporter KCC2 (Rivera et al. 1999, 2005) in the dendrites. Although a similar mechanism may be active in SCs, the whole cell recording configuration of our experiments resulted in a clamped Cl⁻ reversal potential at the soma and thus masked any small change in reversal potential in the dendrites (Fiumelli et al. 2005). For our internal and external solution, the Nernst equation gives a Cl⁻ reversal potential of −72.5 mV. We confirmed this value experimentally, and as expected it did not change after IPSP-spike pairings.

We have shown that timing-dependent plasticity of inhibitory synapses depends on calcium dynamics in the postsynaptic cell and entry of calcium through voltage-gated channels. These results suggest a role for calcium in intracellular processes and mechanisms similar to those involved in plasticity of excitatory synapses. Future experiments will focus on the possible involvement of metabotropic glutamate receptors and endocannabinoids in STDP of inhibitory synapses (Chevaleyre and Castillo 2003) to investigate possible shared or parallel...
mechanisms of excitatory and inhibitory plasticity. We hypothesize that coactivation of glutamatergic and GABAergic inputs could be responsible for the temporal coincidence requirements observed in our data.

One clear function of STDP in excitatory synapses is to increase EPSP-spike efficacy in a postsynaptic target: relevant, causal experience increases the likelihood of successful signal transmission. Inhibitory synapses lack the obvious goal of signal propagation, making the immediate functional consequences of observed plasticity less obvious. However, because inhibition plays a crucial role in modulating and controlling many neuronal processes and rhythms, changes in inhibitory synapses may be as necessary and appropriate as changes in excitatory synapses. Strengthened inhibitory synapses are another way in which cells imprint repeated and correlated causal activity into the connections between neurons. In contrast to excitatory synapses, however, this rule will ultimately inhibit further correlated firing as one of its effects is to inhibit the postsynaptic spike.

Balance between excitation and inhibition seems to play a crucial role for the correct function of neuronal networks throughout the brain (Shu et al. 2003a,b). The plasticity of inhibitory synapses described in this work offers a flexible and efficient mechanism to balance the effects of excitatory STDP. Indeed, the STDP we have shown in inhibitory synapses is likely to cooperate or compete with other forms of STDP in postsynaptic targets. Plasticity measured as a function of field response (Yun et al. 2002) in the EC is likely to be a combined result of multiple forms of single-synapse plasticity, both excitatory and inhibitory. In addition, the EC is a common locus for epilepsy, and recent research highlights the importance of inhibition within layer II in the maintenance of normal circuit function (Bear et al. 1996; Kumar and Buckmaster 2006). Our modeling results show that plasticity of inhibitory synapses offers the EC a degree of flexibility in the inhibitory control of epilepsy.

Modeling studies have suggested potential functions for plastic inhibition in circuit rhythm generation (Soto-Trevino et
al. 2001) and in balancing excitation (Marder and Buonomano 2004). Throughout the brain, inhibitory synapses serve both to modulate excitation in principal neurons and to regulate rhythmic circuits. Our own modeling shows that adjustment in the strength of only a few inhibitory synapses is enough to modulate the overall excitability of an entire layer of neurons. Further, changes in inhibitory strength track changes in excitatory strength autonomously. Extrapolating from our simple models, one might expect plasticity of inhibitory synaptic transmission to exert major influences on neuronal excitability and function.

As shown in our modeling, increases in inhibition may also serve to isolate one cluster of neurons from another by strengthening inhibition at critical locations within the system, thus providing a flexible and dynamic reorganization of neuronal circuitry in the working brain. The timing rule observed is well-poised to enable cluster formation: the temporal peak of potentiation (relative to synaptic delays and response times of neurons) sets a critical radius for activity termination from an originating neuron, as seen in our chain model. Within clusters, where EPSPs arrive before IPSPs, inhibition is suppressed by the depression side of the timing rule. This results in more homogeneous and responsive clusters of SCs.

The observed type of STDP, in which inhibition increases with excitation and activity, can provide a braking mechanism for an unchecked, pathological spread of epileptic-like activity. Indeed, plasticity of inhibition may be crucial to how the brain regulates and controls its own activity.

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