Different Calcium Sources Are Narrowly Tuned to the Induction of Different Forms of LTP

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Raymond, Clarke R. and Stephen J. Redman. Different calcium sources are narrowly tuned to the induction of different forms of LTP. J Neurophysiol 88: 249–255, 2002; 10.1152/jn.00043.2002. The essential role of calcium in the induction of long-term potentiation (LTP) has been well established. In particular, calcium influx via the N-methyl-D-aspartate (NMDA) receptor (NMDAR) is important for LTP induction in many pathways. However, the specific roles of other calcium sources in hippocampal LTP are less clear. The aim of the present study was to determine the appropriate conditions and extent to which non-NMDAR Ca2+ sources contribute to the induction of different forms of LTP in area CA1 of hippocampal slices. Increasing numbers of theta-burst trains (1, 4, and 8 TBS) induced LTP of increasing magnitude and persistence. Inhibition of ryanodine receptors caused inhibition of weak LTP induced by 1 TBS, but had no effect on more robust forms of LTP. Inhibition of IP3 receptors inhibited moderate LTP induced by 4 TBS, but had no effect when 1 TBS or 8 TBS were used. Inhibition of L-type voltage–dependent Ca2+ channels inhibited strong LTP induced by 8 TBS, but had no effect on weaker forms of LTP. These results show that different Ca2+ sources have different thresholds for activation by TBS trains. Furthermore, each Ca2+ source appears to be tuned to the induction of a different form of LTP. Such tuning could reflect an important link between different LTP induction and maintenance mechanisms.

INTRODUCTION

Activity-dependent changes in synaptic efficacy such as long-term potentiation (LTP) are widely believed to underlie learning and memory in the brain (Bliss and Collingridge 1993; Martin et al. 2000). Repetition of high-frequency or patterned stimuli can induce LTP of increasing magnitude and persistence, which in general has been classified as either early-, or late-LTP on the basis of activation of particular biochemical pathways. An extension of this has been proposed based on the finding of three distinct LTP decay time constants in vivo (LTP1, 2, and 3) (Abraham and Otani 1991; Racine et al. 1983), and their reliance on different protein synthesis mechanisms (Otani et al. 1989; Raymond et al. 2000). However, little information is available regarding possible differences in the induction mechanisms of these forms of LTP.

An essential requirement for LTP induction in most neuronal types is an increase in postsynaptic [Ca2+]. In hippocampal CA1 pyramidal cells, the importance of the N-methyl-D-aspartate (NMDA) receptor (NMDAR) for LTP induction has been well established (Bliss and Collingridge 1993). Furthermore, activation of voltage-dependent Ca2+ channels (VDCCs) is important for a seemingly independent form of LTP induced by high-intensity tetanic stimulation (Grover and Teyler 1990; Morgan and Teyler 2001). However, the contribution and conditions under which calcium derived from the internal Ca2+ stores is important for LTP induction in CA1 are less clear (Rose and Konnerth 2001).

The endoplasmic reticulum (ER) constitutes a large and important source of Ca2+ for various neuronal signaling processes (Berridge 1998; Mattson et al. 2000). Ca2+ release from the ER is mediated by two types of receptors, the ryanodine (RyR) and inositol 1,4,5-trisphosphate (IP3R) receptors. RyRs are activated by increases in cytosolic Ca2+ and are predominantly responsible for the phenomenon of Ca2+-induced Ca2+ release (CICR) (Berridge 1998; Zucchi and Ronca-Testoni 1997). IP3Rs are primarily activated by IP3 generated via activation of metabotropic receptors linked to phospholipase C (PLC), although they are also modulated by cytosolic Ca2+ (Berridge 1993, 1998; Simpson et al. 1995). Both types of receptor are widely distributed in the brain, with characteristic patterns in particular regions. In CA1, RyRs are present throughout the neuron, including dendritic shafts and spines, whereas IP3Rs are less predominant in spines but highly expressed in dendritic shafts (Sharp et al. 1993).

There is some evidence that internal Ca2+ stores play a role in LTP induction in the hippocampus. Depletion of ER Ca2+ stores by inhibition of the Ca2+-ATPase pump with thapsigargin has been shown to inhibit LTP, but only under conditions of weak conditioning stimuli (Behnisch and Ryemann 1995; Harvey and Collingridge 1992; Wang et al. 1996). Similarly, targeting RyRs with ryanodine or dantrolene seems only to affect weak LTP (Obenaus et al. 1989; Wang et al. 1996). However, very few pharmacological studies provide specific information on the individual roles of RyRs and IP3Rs in LTP induction in area CA1. Mutations of RyRs have produced conflicting results (Balschun et al. 1999; Futatsugi et al. 1999; Shimuta et al. 2001), and surprisingly, a study of IP3R knockout mice revealed facilitation of LTP induced by very weak stimulation (Fujii et al. 2000).

We sought to investigate the roles of Ca2+ sources other

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than the NMDA receptor in LTP in hippocampal area CA1. Specifically, we studied the effects of pharmacological agents on LTP induction across a range of stimulus protocols to determine the specific conditions under which each Ca²⁺ source is important for LTP induction.

**Methods**

Male Wistar rats (7–8 wk) were anesthetized with halothane and decapitated, and the brains were rapidly removed and submerged in ice-cold artificial cerebrospinal fluid (ACSF, containing, in mM, 124 NaCl, 3.2 KCl, 1.25 NaH₂PO₄, 26 NaHCO₃, 2.5 CaCl₂, 1.3 MgCl₂, and 10 D-glucose, equilibrated with 95% O₂-5% CO₂). Hippocampi were dissected free, and area CA3 was removed by a manual cut to reduce potential hyperexcitability. Transverse hippocampal slices (400 μm) were prepared using a McIlwain tissue sectioner, transferred to a submerged brain slice chamber, and preincubated for at least 2 h in a continuous flow (2 ml/min) of ACSF at 32.5°C.

Extracellular synaptic potentials were recorded from stratum radiatum in area CA1 using glass microelectrodes (2–5 MΩ) filled with 2 M NaCl. Baseline synaptic responses were evoked by stimulation of the Schaffer collateral/commissural pathway at 0.033 Hz (0.1-ms pulse-width) with a Teflon-insulated tungsten monopolar electrode. The stimulation intensity was adjusted to elicit field excitatory postsynaptic potentials (fEPSPs) of approximately two-thirds maximum amplitude. LTP was induced by theta-burst stimulation (TBS), consisting of trains of 10 × 100-Hz bursts (5 pulses/burst) with a 200-ms interburst interval, at the test pulse intensity. One train of 10 bursts is denoted as 1 TBS. When multiple trains were delivered (i.e., 4 TBS and 8 TBS) the intertrain interval was 30 s.

Maximum slopes of fEPSPs were measured off-line and expressed as percentage change from baseline, calculated as the average of the last 15 min of baseline recordings. LTP was measured as the average of the last 10 points in the recording period. Two-tailed Student’s t-tests were performed to determine significance at the 95% confidence level, unless otherwise noted. Data are presented as group means ± SE. Drugs were bath applied via the perfusion medium. Xestospongin C and ryanodine were obtained from Calbiochem (San Diego, CA). Nifedipine was obtained from Sigma (Castle Hill, Australia).

**Results**

**LTP induced by 1, 4, and 8 theta-burst trains**

Previous studies have shown that repetition of a particular conditioning stimulus can induce LTP of increasing magnitude and persistence (Abraham and Huggett 1997; Bliss and Gardner-Medwin 1973; Huang and Kandel 1994). We sought to investigate potential differences in the relative importance of calcium derived from different sources to the induction of LTP by 1, 4, and 8 trains of TBS. In control slices 1 TBS resulted in a weak LTP that rapidly decayed to 4 ± 1% (mean ± SE) at 2 h post-TBS (n = 4, Fig. 1). For this reason, subsequent experiments involving 1 TBS compare LTP at 1 h post-TBS, where potentiation measured 22 ± 5% (n = 8). Increasing the number of TBS trains to 4 resulted in a similar initial level of potentiation, but a slower decay such that LTP measured 18 ± 1% 2 h post-TBS (n = 4, Fig. 1). Finally, 8 TBS resulted in a large initial induction level and a robust LTP measuring 32 ± 6% 2 h post-TBS (n = 6, Fig. 1). These results are similar to those obtained previously using TBS in area CA1 in vitro (Abraham and Huggett 1997; Cohen et al. 1998).

To gain further insight on the differences in LTP induced by each protocol, the post-TBS data for all slices in all control groups were fit with a double exponential decay function, as described previously (Raymond et al. 2000). Data from one slice in the combined 8 TBS group was excluded because an acceptable fit could not be made (χ² test, P < 0.0001). The rate constant of decay of the second, slower exponential was then averaged for each TBS group and used as a measure of LTP persistence. For clarity, the inverse of the mean rate constants for each group were calculated to give the mean decay time constant (τ) in minutes. Increasing the number of TBS trains resulted in LTP of increasing persistence.
statistical analysis was performed on the rate constant data prior to calculation of $\tau$. RY caused a significant increase in the decay of 1 TBS LTP ($\tau = 26$ min, $n = 5$; control (1 h post-TBS group), 69 min, $n = 8$, $P < 0.05$), but had no effect on the decay of either 4 TBS LTP ($\tau = 145$ min, $n = 4$; control, 110 min, $n = 8$) or 8 TBS LTP ($\tau = 288$ min, $n = 4$; control, 230 min, $n = 11$). These results closely match the effects on LTP magnitude and show that inhibition of RyRs prevents the induction of a weak, rapidly decaying form of LTP.

**IP3 receptors**

Until recently, it has been difficult to directly investigate the role of the IP3-sensitive calcium stores in LTP due to the lack of specific pharmacological tools. We have taken advantage of a recently characterized, selective, membrane permeable inhibitor, Xestospongin-C (Xest-C) (Gafni et al. 1997), to test for the involvement of IP3-mediated calcium release in LTP induction by each of the TBS protocols. LTP induced by 1 TBS was not affected by a 10-min application of $5 \mu M$ Xest-C (22 ± 6%, $n = 4$, 1 h post-TBS; control, 22 ± 5%, $n = 8$, Fig. 3B). Similarly, LTP induced by 8 TBS was not significantly affected by Xest-C treatment (29 ± 6%, $n = 4$, 2 h post-TBS).

**Ryanodine receptors**

First, we investigated the role of the ryanodine-sensitive calcium stores in LTP induced by each of the TBS protocols. In these experiments ryanodine (RY, 10 $\mu M$) was bath applied for 10 min prior to, and during, the TBS trains, to inhibit CICR via RY receptors. LTP induced by 1 TBS in the presence of RY was attenuated over the entire time course post-TBS (Fig. 2A and B). At 1 h post-TBS, fEPSPs had returned to baseline levels (2 ± 3%, $n = 5$) and were significantly different from controls (22 ± 5%, $n = 8$, $P < 0.01$). However, RY had no significant effect on LTP induced by either 4 TBS, or 8 TBS (Fig. 2B), with potentiation 2 h post-TBS measuring 24 ± 4% ($n = 4$; control, 18 ± 1%; $n = 4$) and 32 ± 7% ($n = 4$; control, 29 ± 5%; $n = 6$), respectively. RY had no effect on normal synaptic transmission with the difference from baseline fEPSP slope at 1 and 2 h postwash measured 1 ± 2% and -2 ± 1%, respectively ($n = 4$, Fig. 2A).

Since LTP 1, 2, and 3 are defined on the basis of decay rates, the mean time constants ($\tau$) for LTP induced in the presence of RY were calculated and compared with the corresponding control values (Fig. 2C). In this and the following sections,
control, 29 ± 5%, n = 6, Fig. 3B). However, LTP induced by 4 TBS in the presence of Xest-C, decayed more rapidly than controls, and was significantly reduced at 2 h post-TBS (6 ± 3%, n = 5; control, 18 ± 1%, n = 4, P < 0.01, Fig. 3, A and B). Xest-C had no significant effect on normal synaptic transmission over the 2-h postwash recording period (4 ± 2% 2 h postwash, n = 3, Fig. 3A).

Again, the results match the effects on LTP magnitude (Fig. 3C). Data from one slice in the 1 TBS + Xest-C group was excluded because an acceptable fit could not be made (χ² test, P < 0.001). The decay constants for 1 TBS LTP (τ = 58 min, n = 3) and 8 TBS LTP (τ = 208 min, n = 4) were unaffected by Xest-C, whereas 4 TBS LTP decayed significantly faster when induced in the presence of Xest-C (τ = 53 min, n = 5, P < 0.05). Together, these results show that IP3Rs are important for the induction of LTP with moderate magnitude and decay characteristics.

Voltage-dependent calcium channels

In addition to the internal calcium stores, calcium entry through VDCCs could increase cytoplasmic calcium concentration during LTP induction. Indeed, very high-frequency stimulation, or high-intensity theta-burst stimulation, have been shown to induce LTP that is dependent on VDCC activation (Grover and Tyler 1990; Morgan and Teyler 2001). To test for the involvement of L-type VDCCs in LTP induced by each of our TBS protocols, we applied 10 μM nifedipine for 10 min prior to, and during, conditioning stimulation. As expected, nifedipine had no effect on LTP induced by 1 TBS (24 ± 3%, n = 5, 1 h post-TBS; control, 22 ± 5%, n = 8, Fig. 4B). Similarly, 4 TBS-induced LTP was unaffected by nifedipine (20 ± 2%, n = 6, 2 h post-TBS; control, 24 ± 2%, n = 4, Fig. 4B). However, nifedipine caused a dramatic reduction in LTP induced by 8 TBS across the entire post-TBS time course, with potentiation measuring 10 ± 2% 2 h post-TBS (n = 6; control, 32 ± 6%, n = 6, P < 0.01, Fig. 4, A and B). Nifedipine had no significant effect on normal synaptic transmission over the 2-h postwash recording period (4 ± 2% 2 h postwash, n = 3, Fig. 4A).

As before, analysis of decay time constants revealed a close relationship between LTP magnitude and decay (Fig. 4C). The presence of nifedipine during LTP induction had no effect on the decay of 1 TBS LTP (τ = 76 min, n = 5) or 4 TBS LTP (τ = 125 min, n = 6), but significantly enhanced the decay of 8 TBS LTP (τ = 65 min, n = 6, P < 0.05). These results show that L-type VDCCs contribute only to the induction of a robust, slowly decaying form of LTP.

DISCUSSION

The results of our experiments are summarized in Fig. 5A, where the effect of each inhibitor is shown as the percentage inhibition of the control LTP across the three TBS protocols. Thus Fig. 5A illustrates the apparent degree of involvement of ryanodine receptors, IP3 receptors, and VDCCs at each level of LTP.

Thresholds for activation of different calcium sources

An important observation from Fig. 5A is that different calcium sources appear to be activated in sequence, according to particular threshold levels of synaptic activity produced by the TBS protocol. RyRs appear to have the lowest activation threshold, consistent with previous findings that RyRs are involved in LTP induced by very weak stimulation protocols (Behnisch and Reynmann 1995; Harvey and Collingridge 1992; Obenaus et al. 1989). The sensitivity of RyRs to weak synaptic activity is also supported by the finding that single synaptic events can evoke ryanodine-sensitive calcium transients in hippocampal organotypic cultures (Emptage et al. 1999; but see Yuste et al. 1999). In cultures, the RyRs were activated by Ca²⁺ entering via the NMDA receptor. This is also the most likely mechanism for RyR activation in the present experiments, suggesting that, although NMDA receptor activation is often necessary for LTP induction (Bliss and Collingridge 1993), the Ca²⁺ signal is not necessarily sufficient and may be amplified by CICR during low level stimulation.

The present experiments constitute the first direct comparison of the roles of RyRs and IP3Rs in LTP induction. An important finding was that IP3Rs become effective in LTP induced by a higher number of stimulus repetitions than RyRs. Activation of IP3Rs is complicated by the dual-agonist role played by IP3 and cytosolic Ca²⁺ (Berridge 1993, 1998). The
FIG. 5. Narrow tuning of RyRs, IP3Rs, and L-type voltage-dependent Ca\(^{2+}\) channels (VDCCs) for induction of different levels of LTP. A: summary plot of the degree of inhibition caused by ryanodine (green), Xestospongin-C (blue), and nifedipine (red) on LTP induced by 1, 4, or 8 TBS. Data are expressed as the percent inhibition from the respective control LTP value for each protocol. Lines connecting the values for each antagonist illustrate basic "tuning" curves of Ca\(^{2+}\) sources across the 3 protocols. RyRs are tuned to weak LTP induced by 1 TBS, IP3Rs are tuned to moderate LTP induced by 4 TBS, and L-type VDCCs are important only for stronger forms of LTP (*P < 0.01, significant difference from control, Student’s t-test). B: schematic diagram describing a possible relationship between the number of TBS trains and Ca\(^{2+}\) signals from RyRs (green), IP3Rs (blue), and VDCCs (red). Activation thresholds and relative Ca\(^{2+}\) contributions are ordered as follows, RyRs < IP3Rs < VDCCs. Thus the more easily a Ca\(^{2+}\) source is activated, the smaller its Ca\(^{2+}\) signal. Each level of LTP requires a particular threshold level of Ca\(^{2+}\), and these thresholds are matched to the signals provided by individual sources. Inhibiting a "weaker" source during stimulation above threshold for a "stronger" one has no effect on LTP because the weaker signal becomes redundant. C: schematic diagram describing an alternative relationship between TBS trains and Ca\(^{2+}\) signals. Activation thresholds are as described in B, but the relative magnitudes of the Ca\(^{2+}\) signals from each source are not important. In this case, each source is closely linked to an effector system specific for a given form of LTP. Furthermore, blocking RyRs during 4 TBS will have no effect on LTP because RyRs are inhibited at that level of stimulation. Similarly, IP3Rs are inhibited by 8 TBS.

Tuning of calcium sources to different levels of LTP

A second notable feature of the data illustrated in Fig. 5A is that each calcium source is important only within a relatively narrow range of stimulus trains. Thus, as well as having different activation thresholds, the importance of each Ca\(^{2+}\) source in LTP induction diminishes as the number of TBS trains increases beyond a preferred level. One explanation for this phenomenon is that calcium sources may remain active, but their relative contributions to LTP may become redundant as the number of TBS trains increases and other sources become active (Fig. 5B). Alternatively, as the threshold for one Ca\(^{2+}\) source is reached, sources with lower activation thresholds may be inhibited (Fig. 5C).

In the scenario outlined in Fig. 5B, some characteristic of the Ca\(^{2+}\) signal (e.g., magnitude or time integral) from each source is the major determinant of the level of LTP induced. This type of scenario has been proposed to explain how Ca\(^{2+}\) acts as the induction signal for both LTP and long-term depression (LTD), with LTD induced by a “weaker” Ca\(^{2+}\) signal than LTP (Artola and Singer 1993; Lisman 1994). In the present case, calcium sources with higher activation thresholds, once activated, could contribute relatively more to the overall signal, thereby reducing the importance of ongoing signals from more easily activated sources. In the alternative scenario (Fig. 5C), each source contributes similar levels of Ca\(^{2+}\), but is closely associated with a unique effector system underlying a particular form of LTP. The apparent lack of involvement of RyRs and then IP3Rs in LTP induction could therefore be due to 1) a requirement for a high level, or prolonged period of glutamate release to activate perisynaptically located mGluRs (Lujan et al. 1996; Scanziani et al. 1997) and raise the IP3 concentration sufficiently, or 2) a requirement to raise cytosolic Ca\(^{2+}\) to an optimal level for IP3 activation of the receptors. Previous findings that group I mGluRs are important for LTP induced by particular protocols provided indirect evidence of a role for IP3Rs (Raymond et al. 2000; Wilsch et al. 1998). Our findings confirm and extend previous results, providing direct evidence of a requirement for IP3R activation only in LTP of similar magnitude and persistence to that reported to be mGluR sensitive.

The finding that L-type VDCCs do not contribute significantly to LTP until the highest number of stimulus repetitions are used is consistent with the very high-frequency or high-intensity stimulation required to induce VDCC-LTP (Grover and Teyler 1990; Morgan and Teyler 2001). However, the question is raised why repetition of TBS trains spaced at 30-s intervals should be an effective stimulus for activating VDCCs, when a single train does not appear to be? One explanation could be that during 8 TBS, early TBS trains induce NMDA receptor–dependent LTP of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) currents, thereby allowing subsequent trains to reach the threshold for VDCC activation (Morgan and Teyler 2001). Alternatively, some aspect of preceding trains could “prime” VDCCs for activation by subsequent trains (i.e., metaplasticity) (see Abraham and Tate 1997).
our observations if Ca\(^{2+}\) concentrations increased appropriately during repetitive TBS trains.

It should be noted that these models do not make any assumptions about whether the various calcium sources are contributing to NMDAR-dependent or -independent forms of LTP. In fact, the present results suggest that the NMDA/non-NMDA nomenclature may be misleading and that rather there may be several LTP types, each associated with its own specific induction-maintenance pathway. Interestingly, inhibition of non-NMDA calcium sources during LTP induction can interfere with persistence without effect on the initial level of potentiation (see Fig. 3). These findings are consistent with the idea that different non-NMDA calcium signals are more important for the induction of long-term potentiation per se, and that NMDAR activation alone may only induce STP or very weak LTP (Borroni et al. 2000; Cavus and Teyler 1996; Morgan and Teyler 2001). Nonetheless, the models presented here deal with the coding mechanism that links non-NMDA calcium signals to different levels of LTP, and their usefulness in this regard is not affected by the role of the NMDA receptor in LTP.

**Linking LTP induction and maintenance**

In either scenario outlined above, an important implication is that each Ca\(^{2+}\) source appears to be uniquely associated with LTP of particular magnitude and persistence. Thus it may now be possible to classify LTP according to induction mechanisms as well as maintenance mechanisms. Under current classification, LTP is defined on the basis of maintenance. Early-LTP (or LTP1) is short lasting and involves posttranslational modifications on the basis of maintenance. Early-LTP (or LTP1) and late-LTP induction (or LTP2/3) is of greater magnitude and persistence and requires activation of protein synthesis pathways (Abraham and Otani 1991; Krug et al. 1984; Nguyen et al. 1994; Raymond et al. 2000). In the present results, there is a visible correlation between the LTP associated with RyRs, IP3Rs, and VDCCs and LTP 1, 2, and 3 as described in vitro. It is possible therefore that during LTP induction, each Ca\(^{2+}\) source is tuned to activate its own specific LTP maintenance mechanism, whether by virtue of the characteristics of the Ca\(^{2+}\) signal, or the association of Ca\(^{2+}\) channels and effectors in discrete microdomains. This has the effect of blurring the traditional distinction between LTP induction, expression, and maintenance, and invokes the concept of LTP type-specific intracellular pathways that are selectively activated by particular patterns of afferent activity.

RyRs are prominent in dendritic spines of CA1 pyramidal neurons, whereas IP3Rs are virtually absent from these structures. On the other hand, IP3Rs are highly expressed in the dendritic shafts of CA1 pyramidal neurons, whereas RyRs are less prominent and are mostly observed in patches immediately adjacent to spines (Sharp et al. 1993). These expression patterns could provide sufficient compartmentalization to enable differentiation between RyR- and IP3R-mediated signals in these neurons. The presence of RyRs in spines may give them unique access for activating kinases associated with the postsynaptic density that might underlie LTP1 (e.g., CaMKII) (Lisman and Zhabotinsky 2001). In dendritic shafts, IP3Rs may be well placed to activate the mGlurD-dependent, local protein synthesis underlying LTP2 (Raymond et al. 2000). In area CA1, L-type VDCCs are predominantly located on the soma and proximal dendrites (Hell et al. 1996; Magee and Johnston 1995; Westenbroek et al. 1990), and their blockade prevents both late-LTP and associated increases in CRE-mediated gene expression (Impey et al. 1996). Furthermore, behavioral studies suggest that LTP induced by VDCC activation during hippocampal-dependent learning is important for long-term memory (Borroni et al. 2000).

In conclusion, although activation of NMDA receptors is known to be important for LTP induction in area CA1, our results show that other Ca\(^{2+}\) sources make an important contribution. Ryanodine receptors, IP3 receptors, and voltage-dependent calcium channels appear to have different thresholds for activation by LTP-inducing stimuli. Furthermore, selective activation of RyRs, IP3Rs, or VDCCs by conditioning stimuli of different durations appears to enable induction of specific levels of LTP. Such “tuning” could reflect strong links between different Ca\(^{2+}\) sources and LTP maintenance processes, and provide a mechanism allowing particular patterns of afferent activity to selectively induce different phases of LTP.

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