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Two sides to long-term potentiation: a view towards reconciliation

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Almost since the discovery of long-term potentiation (LTP) in the hippocampus, its locus of expression has been debated. Throughout the years, convincing evidence has accumulated to suggest that LTP can be supported either presynaptically, by an increase in transmitter release, or postsynaptically, by an increase in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor number. However, whereas postsynaptic enhancement appears to be consistently obtained across studies following LTP induction, presynaptic enhancement is not as reliably observed. Such discrepancies, along with the failure to convincingly identify a retrograde messenger required for presynaptic change, have led to the general view that LTP is mainly supported postsynaptically, and certainly, research within the field for the past decade has been heavily focused on the postsynaptic locus. Here, we argue that LTP can be expressed at either synaptic locus, but that pre- and postsynaptic forms of LTP are dissociable phenomena mediated by distinct mechanistic processes, which are sensitive to different patterns of neuronal activity. This view of LTP helps to reconcile discrepancies across the literature and may put to rest a decades-long debate.

1. Long-term potentiation expression at the pre- and postsynaptic locus is mechanistically distinct

While the locus of long-term potentiation (LTP) expression is disputed, the locus of LTP induction is widely accepted to be postsynaptic and dependent on *N*-methyl-D-aspartate receptors (NMDARs). Blockade of NMDARs is often reported to inhibit LTP induction [1], and Ca^{2+} influx from the receptor has been causally linked to the insertion of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) [2]. NMDARs, however, are not always required for the induction of LTP. In 1990, Grover & Teyler [3] reported that LTP could be induced in NMDAR blockade (50 µM (2*R*)-amino-5-phosphonovaleric acid (APV)) with 200 Hz, but not 100 Hz, tetanic stimulation; potentiation was not simply a result of residual NMDAR activity during high-frequency stimulation as it was induced with similar magnitude under a more potent receptor blockade (100 µM APV + 20 µM MK-801) ([4] but see [5]). LTP obtained in NMDAR blockade was later shown to require the activation of L-type voltage-gated calcium channels (L-VGCCs) [6–11]. Others subsequently reported that a similar form of potentiation could be obtained (i) when presynaptic stimuli (less than or equal to 0.1 Hz) were delivered in the presence of voltage-gated potassium channel blockers [6,8,9,11–13], (ii) when tetanic stimulation (25–100 Hz) occurred in the absence of gamma aminobutyric acid A ($GABA_A$)-mediated inhibition [14,15] and (iii) when presynaptic stimuli (1–2 Hz) were paired with strong postsynaptic depolarization [7,16]; by contrast, no potentiation was induced by presynaptic stimulation in the absence of postsynaptic depolarization or by postsynaptic depolarization in the absence of presynaptic stimulation [4,17]. These findings suggest that the induction of L-VGCC-dependent LTP requires presynaptic activity to coincide with strong postsynaptic depolarization, and that given strong postsynaptic depolarization, LTP can be induced even with very low-frequency (less than or equal to 0.1 Hz) presynaptic stimulation. Although it may be thought that the stimulation paradigms used to obtain L-VGCC-dependent LTP represent artificial experimental conditions that would be unlikely to occur *in vivo*, several groups have also shown that L-VGCC-dependent LTP can be induced by theta-burst stimulation [10,18–21], which is thought to emulate

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physiological patterns of hippocampal activity. Moreover, the finding that inhibition of L-VGCCs augments the impairment to spatial memory caused by NMDAR antagonists, suggests that L-VGCCs support some aspects of learning and memory *in vivo*, independent of NMDARs [22–24].

The locus of expression of L-VGCC-dependent LTP appears to be presynaptic [16,20,25] (but see [4]). The most compelling evidence comes from Bayazitov *et al*. [20], who used synaptopHlourins to optically monitor activity-driven changes in presynaptic function [20]. SynaptopHlourin is a pH-sensitive variant of green fluorescent protein that has been fused to the luminal domain of the vesicular protein, VAMP2. The fluorophore is quenched within the acidic lumen of the vesicle and fluoresces upon vesicular exocytosis, when it is exposed to the pH-neutral extracellular environment. Bayazitov *et al*. [20] demonstrated that presynaptic function was enhanced following either theta-burst or 200 Hz stimulation and that such increases could only be abolished with the L-VGCC antagonist, nitrendipine, but not with the NMDAR antagonist, APV; the resilience of presynaptic enhancement to APV is also evident in several studies using FM dyes to monitor presynaptic function [18,26,27]. Moreover, in APV, a similar fold potentiation was observed both for the presynaptic pHlourin response and the recorded field potential, suggesting that LTP was exclusively expressed presynaptically under NMDAR blockade. Conversely, tetanus in nitrendipine resulted in an enhancement of the recorded field potential but not in the presynaptic pHlourin response, suggesting that under L-VGCC blockade, LTP was exclusively expressed postsynaptically. Such findings strongly suggest that pre- and postsynaptic forms of LTP are mechanistically distinct, with the former requiring L-VGCC activation and the latter requiring NMDAR activation.

The finding that presynaptic change can occur independently of NMDAR activation appears to be at odds with findings from other laboratories, including our own, that demonstrate that NMDAR blockade abolishes, or at least reduces, presynaptic enhancement [18,20,26–28]. It is, however, important to recognize that the NMDAR, in addition to acting as a Ca^{2+} source for the spine, is also a potent source of depolarization for the cell and dendrite. The NMDAR is far more permeable to Na^{+} than it is to Ca^{2+}, and the activation of the receptor facilitates somatic and dendritic spiking [14,29–32]. Although postsynaptic enhancement depends on NMDARs as a source of Ca^{2+}, presynaptic enhancement, given its dependence on L-VGCC activation, may only rely on NMDARs as a source of postsynaptic depolarization. This would explain why NMDAR antagonists abolish presynaptic potentiation during standard 100 Hz, but not during 200 Hz or theta-burst stimulation protocols, which are more effective at producing postsynaptic depolarization via AMPAR activation. It is important to note that presynaptic potentiation can also be obtained when single presynaptic stimuli are paired with postsynaptic depolarization, which rules out any specific requirement of high-frequency presynaptic activity for the enhancement of presynaptic strength [16,33]. Thus, pre- and postsynaptic forms of LTP may well be mechanistically dissociable and differentially depend on L-VGCCs and NMDARs for Ca^{2+} influx.

2. Reconciling the literature

The inconsistency with which presynaptic changes are reported across laboratories has cast doubt as to whether the presynaptic terminal is a locus of LTP expression. However, given the differential importance of L-VGCC activation in pre- and postsynaptic forms of LTP, the failure of some laboratories to report presynaptic enhancement might depend on the nature of the experimental conditions under which LTP is induced. L-VGCCs are activated by strong depolarization and are susceptible to desensitization during periods of prolonged depolarization (more than 100 ms) [34,35]. As such, we reason that the magnitude and duration of postsynaptic depolarization during LTP induction determines the extent of L-VGCC activation, and thus the likelihood that LTP has a presynaptic component of expression. To test this idea, we examined past studies to see whether a correlation exists between the stimulation protocol used to induce LTP and the likelihood of obtaining presynaptic enhancement. To circumvent bias, our literature search was guided by past reviews on the locus of LTP expression [2,36–42], including those predominantly supporting either a pre- [39] or postsynaptic view [2,36,37]. Collectively, the studies included in our analysis employed a variety of techniques to investigate the locus of LTP expression at Schaffer-collateral synapses, including the use of: the NMDAR-component of synaptic potentials, glial transport currents, use-dependent-receptor blockers to estimate glutamate release probability, paired pulse ratios or brief high-frequency bursts to monitor changes in short-term plasticity, and finally, FM dyes, Ca^{2+} indicators or pHlourins to optically monitor presynaptic function. We excluded studies using coefficient of variation analysis, minimal stimulation or paired recordings, principally because the unmasking of postsynaptically silent synapses can masquerade as presynaptic enhancements using these techniques. Postsynaptic unmasking contributes significantly to LTP expression, especially during the first few weeks of postnatal development, when synaptic plasticity is most commonly studied [43]. It is therefore difficult to judge whether changes in coefficient of variation analysis or in synaptic failure rate following LTP induction in young tissue are attributable to the enhancement of pre- or postsynaptic function. Moreover, results from minimal stimulation are potentially confounded by activity-dependent changes in axonal excitability for experiments conducted at room temperature ([44] but see [45]).

We examined a total of 38 studies, which assess LTP expression across 53 experimental conditions (table 1). Presynaptic changes were reported in 23 of the 38 studies and in 23 of the 53 experimental conditions. LTP was generally induced either by brief, high-frequency tetanic stimulation (50–200 Hz) or by a pairing protocol, in which lower frequency stimulation (generally less than 2 Hz but ranging between 0.2 and 100 Hz) was delivered while voltage-clamping the postsynaptic neuron between −10 and 10 mV, often for tens of seconds. From our meta-analysis, we find that LTP is significantly more likely to have a presynaptic component of expression when induced by tetanic stimulation (20 of 35 conditions) rather than by pairing (3 of 18 conditions) ($X^2 = 7.92$; $p = 0.005$). LTP induced by pairing, rather than tetanic stimulation, also appeared to be insensitive to L-VGCC blockers [7,10,18–20]. Perhaps, one reason for these findings is that prolonged periods of depolarization that are involved in pairing protocols, although effective at relieving the Mg^{2+} block of NMDARs, may desensitize L-VGCCs; the resulting LTP is therefore insensitive to L-VGCC antagonists and lacks a presynaptic component of expression. That said, pairing protocols can elicit L-VGCC-dependent LTP when postsynaptic depolarization consists of several brief, rather than one long,

Table 1. Studies examining the presynaptic expression of LTP. NMDAR, NMDA-receptor-mediated component of synaptic response; SRP, synaptic refractory period; STP, short-term plasticity; GTC, glial transport current; PPR, paired pulse ratio; DNXQ, 6,7-dinitroquinoxaline-2,3-dione; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione.

citation[a]	method	protocol	%LTP[b]	Δpre[c]	additional notes
tetanus-induced LTP					
Muller & Lynch [46]	NMDAR	(4 at 100 Hz) × 10 at 5 Hz	163	yes (119%)	LTP induced in low Mg^{2+}
Muller *et al*. [47,48]	NMDAR	(4 at 100 Hz) × 10 at 5 Hz	130	no	LTP induced in low Mg^{2+}
	NMDAR	(4 at 100 Hz) × 10 at 5 Hz	120	yes (120%)	LTP induced in low Mg^{2+} and DNQX
Muller *et al*. [49]	NMDAR	(4 at 100 Hz) × 10 at 5 Hz	148	no	NMDAR assessed using bursts (4 at 100 Hz)
Bashir *et al*. [50]	NMDAR	25 at 100 Hz	143	yes (143%)	LTP induced in CNQX
Asztely *et al*. [51]	NMDAR	10 at 50 Hz	114	yes (114%)	LTP induced in low Mg^{2+} and CNQX
Clark & Collingridge [52]	NMDAR	100 at 100 Hz	160	yes (160%)	
Kullmann *et al*. [53]	NMDAR	(5 at 100 Hz) × 50 at 5 Hz	150	yes (120%)	
Mainen *et al*. [54]	NMDAR	(50–100 at 100 Hz) × 1–3	265	no	GluR2 knockout mouse
	polyamine use-dependent block	(50–100 at 100 Hz) × 1–3	254	no	GluR2 knockout mouse
Muller & Lynch [55]	PPR	(4 at 100 Hz) × 10 at 5 Hz	150	no	
Zalutsky & Nicoll [56]	PPR	(100 at 100 Hz) × 4 at 0.1 Hz	163	no	
Foster & McNaughton [57]	PPR	(8 at 400 Hz) × 4	125	no	
Schulz *et al*. [58]	PPR	(50 at 100 Hz) × 10 at 5 Hz × 1–6	179	yes	
Schulz [59]	PPR + other occlusion/rescue experiments	(50 at 100 Hz) × 10 at 5 Hz × 1–6	250	yes	see reference for more details on occlusion/rescue exps.
Kleschevnikov *et al*. [60]	PPR	100 at 100 Hz (strong)	280	yes	
	PPR	100 at 100 Hz (weak)	150	no	
Volianskis & Jensen [61]	PPR	(4 at 100 Hz) × 10 at 5 Hz	160	yes	
Pananceau *et al*. [62]	STP and PPR	(25 at 200 Hz) × 5	214	no	STP assessed w/5 at 20 and 50 Hz
Yasui *et al*. [63]	STP	50–100 at 100 Hz	144	yes	STP assessed w/10 at 10 Hz
Volianskis *et al*. [64]	STP	(4 at 100 Hz) × 10 at 5 Hz	180	yes	STP assessed w/7 at 12.5 Hz; decayed 2 h post-tetanus
Luscher *et al*. [65]	GTCs	(50 at 50 Hz) × 4 at 0.05 Hz OR (100 at 50 Hz) × 4 at 0.05 Hz	159	no	LTP induced in CNQX
	GTC	(100 at 50 Hz) × 4 at 0.05 Hz	179	no	
Diamond *et al*. [66]	GTC	(100 at 100 Hz) × 3	170	no	
Johnstone & Raymond [67,68]	FM-dye	((5 at 100 Hz) × 10 at 5 Hz) × 1	130	no	
	FM-dye and PPR	((5 at 100 Hz) × 10 at 5 Hz) × 4 at 0.0033 Hz	180	yes	
	FM-dye and PPR	((5 at 100 Hz) × 10 at 5 Hz) × 8 at 0.0033 Hz	184	yes	

(*Continued*.)

Table 1. (*Continued.*)

citation[a]	method	protocol	%LTP[b]	Δpre[c]	additional notes
Zakharenko *et al*. [18,19]	FM-dye	50 at 50 Hz	129	no	
	FM-dye	(100 at 100 Hz) × 4 at 0.05 Hz	154	no	
	FM-dye	(40 at 200 Hz) × 10 at 0.2 Hz	185	yes	
	FM-dye	((4 at 100 Hz) × 5 at 5 Hz) × 3 at 0.0033 Hz	210	yes	
Bayazitov *et al*. [20]	pHlourin	(40 at 200 Hz) × 10 at 0.2 Hz	200	yes	pHlourin response assessed w/50 at 10 Hz
	pHlourin	((4 at 100 Hz) × 5 at 5 Hz) × 3 at 0.0033 Hz	220	yes	pHlourin response assessed w/50 at 10 Hz
Emptage *et al*. [28], Ward *et al*. [69]	Ca^{2+} imaging and PPR	(20 at 100 Hz) × 3 at 0.75 Hz	265	yes	
Enoki *et al*. [33]	Ca^{2+} imaging	(20 at 100 Hz) × 3 at 0.75 Hz OR 100 at 0.003 Hz, each paired with three postsynaptic spikes	199	yes	
pairing-induced LTP					
Perkel & Nicoll [70]	NMDAR	(100 at 100 Hz) × 2 at 0.1 Hz	175	no	LTP induced in CNQX
	NMDAR	40 at 2 Hz; 0 mV	190	no	LTP induced in CNQX
	NMDAR	50 at 0.5–0.7 Hz; 30 mV	165	no	
Kauer *et al*. [71]	NMDAR	19 at 2 Hz; 0 mV	150	no	LTP induced in CNQX
	NMDAR	(100 at 100 Hz) × 2 at 0.05 Hz; 0 mV	180	no	LTP induced in CNQX
	NMDAR	(100 at 100 Hz) × 2 at 0.05 Hz; 0 mV	152	no	
Plant *et al*. [72]	NMDAR	50–100 at 0.5–2 Hz; −10 to 0 mV	155	no	
Kullmann *et al*. [53]	NMDAR	120 at 2 Hz; 0 mV	162	yes (110%)	
	MK801	100 at 100 Hz × 2; 0 mV	162	yes	use-dependent block
Manabe & Nicoll [73]	MK801	40 at 2 Hz; 0 mV	158	no	use-dependent block
Manabe *et al*. [74]	PPR	80 at 2 Hz; 0 mV	178	no	
	PPR	100 at 100 Hz; 0 mV	178	no	
Palmer *et al*. [45]	PPR	40 at 0.5 Hz; 0 mV	234	yes	P6 rodent slices
	PPR	40 at 0.5 Hz; 0 mV	223	no	P12 rodent slices
Hjelmstad *et al*. [75]	SRP	100 at 1 Hz; 0 mV	200	no	SRP probed w/2 at 250 Hz
	SRP	(100 at 100 Hz) × 2 at 0.67 Hz; 0 mV	200	no	SRP period probed w/2 at 250 Hz
	4-AP occlusion	((100 at 100 Hz) × 2 at 0.67 Hz) × 5; 0 mV	260	no	
Selig *et al*. [76]	STP	120 at 1 Hz; −10 mV	286	no	STP assessed w/7 at 25 Hz

[a]Blank spaces represent additional experiments conducted by same study cited in the row above. Studies with very similar experimental conditions have been combined and are represented in one row.

[b]% LTP is expressed as % of baseline measured 30 min post-tetanus. %LTP was estimated from graphs in studies where LTP magnitude was not mentioned in the text. In instances where a study conducted multiple experiments under similar conditions, %LTP was taken as the average across experiments.

[c]Quantitative changes in presynaptic efficacy were reported in some studies and are shown in brackets where appropriate.

voltage step; this protocol may more effectively activate L-VGCCs without triggering channel desensitization [7].

Tetanic stimulation did not always produce presynaptic changes. However, given the high voltage-threshold property of L-VGCCs, the likelihood of generating presynaptic potentiation would depend on the ability for tetanus to produce sufficiently strong postsynaptic depolarization. Consistent with this, Zakharenko *et al*. [18,19] and Bayazitov *et al*. [20] demonstrated, using optical techniques, that theta-burst or 200 Hz stimulation generated an L-VGCC-sensitive form of LTP involving robust presynaptic enhancements, whereas no such L-VGCC-sensitive enhancements were induced by 50 or 100 Hz stimulation [18–20,25]. As stated previously, the enhanced probability of obtaining presynaptic changes under high-frequency stimulation probably reflects the requirement for strong postsynaptic depolarization rather than for high-frequency presynaptic activity *per se* [6–11,16, 33]. Other experimental conditions may also influence the level of postsynaptic depolarization achieved during tetanus including the temperature of the preparation, the divalent cation concentration, $GABA_A$-receptor antagonists, as well as the intensity and duration of presynaptic stimulation used during tetanus, all of which vary considerably across studies. As such, tetanic stimulation might preferentially generate presynaptic enhancement under some experimental conditions, but not others.

We further examined whether the magnitude of LTP generated by tetanic stimulation reflects the likelihood that LTP is associated with presynaptic enhancement, regardless of the actual pattern of stimulation and the experimental conditions under which it is induced. We reason that stimulation achieving sufficiently strong depolarization would recruit both pre- and postsynaptic components of LTP, and therefore generate larger enhancements in synaptic activity. Consistent with this notion, we find that the average amplitude of LTP was $194.59 \pm 9.62\%$ ($n = 17$) when it was associated with presynaptic enhancement, but only $153.50 \pm 7.77\%$ ($n = 12$) when it was not ($U = 34$; $p = 0.003$) (figure 1). Moreover, presynaptic enhancement was reported in 91.67% of experiments ($n = 11/12$) that produced LTP with a magnitude greater than or equal to 180% (figure 1; dashed line), but only 35.3% of experiments ($n = 6/17$) produced LTP with a lower magnitude ($X^2 = 9.21$; $p = 0.002$). Only experiments that induced LTP using tetanic stimulation under standard experimental conditions were included in our analysis (29 of 35 conditions); as such, experiments in which LTP was induced in AMPAR blockade or in GluR2 knockout animals were excluded (6 of 35 conditions). Collectively, these findings demonstrate that LTP at the presynaptic terminal is not some enigmatic and sporadic process, but a predictable form of plasticity whose induction is likely to depend on the levels of postsynaptic depolarization achieved during tetanus.

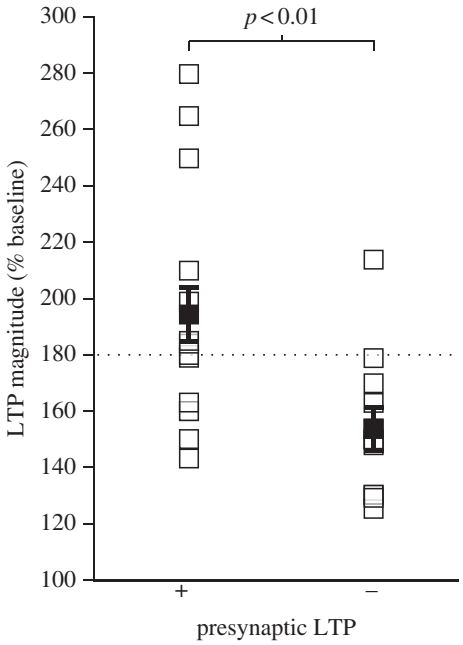

Figure 1. LTP magnitude predicts a presynaptic component of expression. LTP magnitude following tetanic stimulation is shown for 29 experimental conditions, 17 of which report a presynaptic component of expression (+). LTP with a magnitude greater than or equal to 180% (dashed line) had a higher probability of being associated with a presynaptic component of expression (91.67%) than LTP with a lower magnitude (35.3%).

3. Nitric oxide as a retrograde messenger

LTP at the presynaptic locus is dependent on postsynaptic depolarization. How this event is signalled is not known, but it is thought to depend on a postsynaptically generated retrograde signal. Unfortunately, the failure to identify a convincing messenger has cast doubt on a presynaptic locus of LTP. Although several putative messengers have been proposed [25,77,78], the most commonly investigated candidate has been, and continues to be, nitric oxide (NO). NO was first suggested as a retrograde signal in plasticity by Schuman & Madison [79] and O'Dell *et al*. [80], who demonstrated that inhibition of NO signalling impaired the induction of LTP, a finding that had been previously reported by Bohme *et al*. [81]. Similar impairments in LTP could be achieved by scavenging extracellular NO using haemoglobin, suggesting that NO was required to act across the synapse to potentiate synaptic responses [79]. The inherently diffuse nature of NO signalling would appear to contradict the site-specificity of LTP. Zhuo *et al*. [82,83], however, demonstrated that NO application had no effect on synaptic responses until paired with a weak tetanus, which alone failed to generate LTP, suggesting that NO was only effective at potentiating responses at active synapses [82,83]. Subsequent studies demonstrated that NO synthesis is activity dependent and that both neuronal and endothelial variant of nitric oxide synthase (NOS) are expressed postsynaptically in CA1 pyramidal neurons [84], and that genetic deletion of NOS [85–87], or pharmacological inhibition of NOS *in vivo* [88], impairs LTP at Schaffer-collateral synapses.

Perhaps, the most compelling evidence for NO as a retrograde messenger came in 1996, from Arancio *et al*. [89]. In their study, the authors demonstrated that LTP induction was blocked by (i) extracellular NO scavengers, (ii) intracellular NO scavengers applied to either pre- or postsynaptic neurons and (iii) injection of NOS inhibitors in the post-, but not pre-, synaptic neuron. They further showed (i) that photolytic release of NO could generate LTP when paired with presynaptic stimulation (ii) and that potentiation could be blocked by extracellular NO scavengers when NO was photoreleased in the post-, but not presynaptic compartment. Their findings strongly suggest that extracellular diffusion of postsynaptically synthesized NO into active presynaptic terminals is both necessary and sufficient for the induction of LTP.

Table 2. Studies examining the involvement of nitric oxide in LTP. SD, Sprague-Dawley.

citation[a]	protocol	%LTP[b]	ΔLTP in NO blockade[c]	age/animal	temp. (°C)	NO inhibitors[d]
Bohme *et al*. [81]	(100 at 100 Hz × 2) at 0.02 Hz	146	decreased (9%)	5–6 weeks SD	32°C	L-NoArg (0.1 μM)
Schuman & Madison [79]	(100 at 100 Hz) × 4–5 at 0.033–0.066 Hz	143	decreased (0–10%)	2–3 weeks SD	22°C	L-NoArg (100 μM), L-MeArg (100 um), Hg (100 μM)
O'Dell *et al*. [80]	(100 at 100 Hz) × 2 at 0.05 Hz	205	decreased (20%)	Age? Guinea pig	24°C	L-NoArg (50 μM), L-MeArg (1000 um intracellular), Hg (20 μM)
Bon *et al*. [92]	(100 at 100 Hz × 2) at 0.02 Hz	200	decreased (43%)	5–6 weeks SD	32°C	L-NoArg (0.1–100 nM), Hg (10–100 nM)
Gribkoff & Lum-Ragan [93]	(100 at 100 Hz); 50% max intensity	135	no change (40%)	4–12 weeks F-344 male rat	32°C	L-NoArg (50–200 μM), NMMA (100 μM)
	100 at 100 Hz × 2) at 0.017 Hz; max intensity	190	decreased (25%)	4–12 weeks F-344 male rat	32°C	L-NoArg (100 μM), NMMA (100 μM)
Haley *et al*. [94]	(4 at 100 Hz) × 10 at 5 Hz	137	decreased (2%)	4–6 weeks SD	31°C	L-NoArg (10 nM–10 μM), Hg (100 μM)
Haley *et al*. [95]	(25 at 100 Hz) × 2 at 0.2 Hz	119	decreased (6%)	4–6 weeks SD	31°C	L-NoArg (10–1000 μM)
	(50 at 100 Hz) × 2 at 0.1 Hz	115	no change (17%)	4–6 weeks SD	31°C	L-NoArg (10–1000 μM)
	(25 at 100 Hz) × 2 at 0.2 Hz; 2× intensity	118	no change (15%)	4–6 weeks SD	31°C	L-NoArg (10–100 μM)
Kato & Zorumski [96]	30 at 100 Hz	109	increased (33%)	3–4 weeks male albino rat	30°C	L-NoArg (5–100 μM); Hg (10 μM)
Chetkovich *et al*. [97]	100 at 100 Hz × 3 at I0.02 Hz; 50% max intensity	150	decreased (13%)	approximately 4 weeks SD	32°C	L-NoArg (100 μM)
	100 at 100 Hz × 3 at I0.02 Hz; max intensity	175	no change (75%)	approximately 4 weeks SD	32°C	L-NoArg (100 μM)
Musleh *et al*. [98]	(4 at 100 Hz) × 10 at 5 Hz	142	decreased (−8%)	4–6 weeks SD	35°C	L-NoArg (20 μM), L-MeArg (100 μM), Hg (50 μM)
Williams *et al*. [99]	(20 at 100 Hz) × 6 at 0.33 Hz	130	decreased (0%)	5–7 weeks SD	24°C	L-NoArg (100 μM) L-NAME (0.1 mM), Hg (20 μM)
	(20 at 100 Hz) × 6 at 0.33 Hz	180	decreased (22%)	5–7 weeks SD	24°C	L-NoArg (100 μM)
	(20 at 100 Hz) × 6 at 0.33 Hz+Bicuculline	156	no change (60%)	5–7 weeks SD	29°C	L-NoArg (100 μM)
	(20 at 100 Hz) × 6 at 0.33 Hz	159	no change (56%)	16–24 weeks SD	29°C	L-NoArg (0.1–1 mM), L-NAME (0.1 mM), Hg (20 μM)

(*Continued*.)

Table 2. (*Continued.*)

citation[a]	protocol	%LTP[b]	ΔLTP in NO blockade[c]	age/animal	temp. (°C)	NO inhibitors[d]
Nicolarakis & Bennett [100]	(50 at 100 Hz) × 2 at 0.1 Hz	192	decreased (32%)	3–5 weeks Wistar	21–23°C	L-NAME (100–300 μM)
Cummings *et al.* [101]	(100 at 100 Hz) × 4 at 0.033 Hz	150	decreased (56%)	2–3 weeks SD	25–29°C	L-NoArg (100 μM)
O'Dell *et al.* [86]	(4 at 100 Hz) × 25 at 5 Hz; baseline intensity	125	decreased (5%)	Age? mouse	30°C	L-NoArg (50 μM)
	(4 at 100 Hz) × 25 at 5 Hz; 50% max intensity	190	decreased (60%)		30°C	L-NoArg (50 μM),
Boulton *et al.* [102]	100 at 100 Hz	168	decreased (32%)	4–6 weeks? Wistar	24°C	L-NoArg (100 μM)
	100 at 100 Hz	180	decreased (34%)	4–6 weeks? Wistar	30°C	L-NoArg (100 μM)
Malen & Chapman [103]	900 at 30 Hz	123	decreased (3%)	2–20 weeks SD	32°C	L-NAME (100 μM)
	50 at 100 Hz	115	no change (17%)	2–20 weeks SD	32°C	L-NAME (100 μM)
Zhou *et al.* [104,105]	100 at 100 Hz	163	decreased (−6%)	4–6 weeks SD	28–30°C	L-NoArg (100 μM)
	100 at 100 Hz ×2; 2 × baseline duration	210	decreased (81%)	4–6 weeks SD	28–30°C	L-NoArg (100 μM)
Wilson *et al.* [87]	10 at 100 Hz × 3	138	decreased (8%)	8–12 weeks mouse	29–31°C	L-NoArg (200 μM)
	10 at 100 Hz × 3; 2 × baseline duration	150	decreased (40%)	8–12 weeks mouse	29–31°C	L-NoArg (200 μM)
Ko & Kelly [106]	(25 at 100 Hz) × 5 at 0.2 Hz	180	decreased (25%)	5–8 weeks SD	32°C	L-NAME (100 μM), C-PTIO (30 μM), MGD-Fe (75/150 μM)
Bon & Garthwaite [107]	100 at 100 Hz	150	decreased (25%)	6–8 weeks SD	30°C	L-NoArg (100 μM), L-NIO (100 μM)
Johnstone & Raymond [67]	((4 at 100 Hz) × 10 at 5 Hz) × 1	130	no change (35%)	6–8 weeks Wistar	approximately 22°C	L-NAME (100 μM), cPTIO (40 μM)
	((4 at 100 Hz) × 10 at 5 Hz) × 4 at 0.003 Hz	150	no change (60%)	6–8 weeks Wistar	approximately 22°C	
	((4 at 100 Hz) × 10 at 5 Hz) × 8 at 0.0033 Hz	180	decreased (40%)	6–8 weeks Wistar	approximately 22°C	

[a]Blank spaces represent additional experiments conducted by same study cited in the row above. Studies with very similar experimental conditions have been combined and are represented in one row.
[b]%LTP is expressed as % of baseline measured 30 min post-tetanus. %LTP was estimated from graphs in studies where LTP magnitude was not mentioned in the text. In instances where a study conducted multiple experiments under similar conditions, %LTP was taken as the average across experiments.
[c]%LTP obtained with NO inhibition is included in brackets.
[d]L-NoArg, N omega-nitro-L-arginine; L-MeArg, NG-methyl-L-arginine; Hg, haemoglobin; NMMA, L-NG-monomethylarginine; L-NAME, L-NG-nitroarginine methyl ester; C-PTIO, 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide; MGD-Fe, iron-*N*-methyl-D-glucamine dithiocarbamate complex; L-NIO, N5-(1-iminoethyl)-L-ornithine.

Although the study by Arancio *et al*. [89] demonstrates that NO acts at the presynaptic terminal, evidence for its role in the actual enhancement of presynaptic strength has come more recently. In 2003, Nikonenko *et al*. [90] found that tetanic stimulation induced structural changes within the axon, including outgrowth of filopodia and the restructuring of presynaptic boutons. These changes could be abolished with NO inhibitors and could be elicited with bath application of NO donors. Stanton *et al*. [91] later demonstrated that activity-dependent potentiation of presynaptic function, as assessed with FM dyes, was also dependent on NO signalling [91]; these findings have since been confirmed by two additional studies using FM dyes and paired pulse ratio to monitor presynaptic enhancements [27,67].

4. Reconciling the literature

Although NO appears to be a promising candidate for a retrograde signal, its role in plasticity remains controversial, principally because some studies fail to find LTP impairments following the inhibition of NO signalling. Much like the presynaptic expression of LTP, the importance of NO looks to be dependent on the stimulus paradigm used to induce LTP. For example, Johnston & Raymond [68] demonstrated that NO inhibitors only affected LTP induced by multiple trains of theta-burst stimulation, as opposed to a single train, which in their hands failed to enhance presynaptic strength [68]. We therefore reason that NO inhibition is most likely to impair LTP when it has a presynaptic component of expression. To examine this idea, we looked at studies investigating the effects of NO inhibitors on LTP at Schaffer-collateral synapses; all relevant studies searched on PubMed (search terms: LTP and NO) were included. Although, these studies did not specifically monitor presynaptic strength, we looked to see whether, across studies, the sensitivity of LTP to NO inhibitors was correlated with the magnitude of LTP, which we have already shown reflects the likelihood that an enhancement in presynaptic function has occurred post-tetanus (figure 1).

We examined a total of 36 experiments across 21 studies (table 2); experiments were divided into NO-sensitive and NO-insensitive, depending on whether NO blockade reduced the expression of LTP. We find that the magnitude of control LTP is $162 \pm 5.5\%$ in NO-sensitive experiments (25/36), but only $136 \pm 8.0\%$ in NO-insensitive experiments (11/36) ($U = 84.5$; $p = 0.02$). We also divided experiments based on those reporting (i) strong LTP, as defined as having a magnitude greater than or equal to 180%, which has a high probability (91.67%) of being associated with presynaptic changes (figure 1) and (ii) those reporting weak LTP (less than 180%), which is less likely (35.3%) to be associated with presynaptic changes. Although the age and temperature of the preparation, as well as the type and concentration of NO inhibitors varied greatly across experiments (table 2), we find that NO inhibition reduced LTP in 10 of 10 experiments that yielded strong LTP but in only 16 of 26 experiments that yielded weak LTP ($X^2 = 11.08$; $p = 0.0009$). Such findings suggest that the degree to which plasticity is dependent on NO signalling depends on the magnitude, and potentially the locus, of LTP. It should be mentioned, however, that independent of its role as a retrograde signal, NO has effects on postsynaptic signalling; as a result, inhibition of NO synthesis may have additionally affected postsynaptic plasticity under certain experimental conditions [99,103,106,108,109].

There have also been disagreements regarding the effect of exogenous NO on synaptic function. Bohme *et al*. [81] first demonstrated that NO donors persistently potentiated synaptic responses; similar effects were later confirmed using NO donors, free NO, and photoactivated NO [80–83,89,90,92, 103,104]. By contrast, two groups have failed to elicit LTP with NO application [110–112]. Exogenous NO, therefore, appears to have varied effects on synaptic responses across studies. However, it is important to recognize that, like any transmitter in the nervous system, NO has a diverse repertoire of effects on neuronal function [113]. As with glutamate, the specific effect of NO at a synapse will very likely depend on (i) the spatio-temporal dynamics and concentration of signalling, (ii) the current pattern of neuronal activity and (iii) the state of the synapse. For NO, the parameters required for the induction of LTP remain largely unknown and may not always be emulated by the application of exogenous NO, in whatever form [113]. The fact that the vast majority of studies manage to potentiate synaptic responses using exogenous NO, while having little knowledge of the dynamics of endogenous NO signalling, is remarkable in and of itself, and certainly a compelling demonstration that NO signalling has the potential to induce LTP; though, as with glutamate, this potential is likely to be realized only under certain conditions.

5. Concluding remarks

Discrepancies in the literature have raised doubts over a presynaptic locus of LTP. We have argued that these discrepancies actually reflect the presence of two mechanistically distinct forms of LTP: one, which is expressed postsynaptically and dependent on Ca^{2+} influx from NMDARs and the other, which is expressed presynaptically and dependent on Ca^{2+} influx from L-VGCCs. Experimental protocols that successfully activate L-VGCCs are most likely to recruit a presynaptic component of LTP expression and are also most likely to involve a retrograde signal, such as NO. As research continues to elucidate the mechanistic basis of presynaptic plasticity, one thing is becoming clear: the current, postsynaptic-centric dogma of LTP needs to change in order to reflect the more comprehensive understanding of synaptic plasticity that is supported by a growing body of literature. There are two sides to the synapse, and both can change.

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