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Commentary

Central Sensitization Versus Synaptic Long-Term Potentiation (LTP): A Critical Comment

I read with interest the chapter, "Activity-Dependent Central Sensitization and Synaptic Plasticity," in the recent review article by Latrémolière and Woolf[11] in The Journal of Pain. I noticed a number of issues in that chapter which deserve some discussion. These include the concept of synaptic long-term potentiation in pain pathways and its relation to the more general phrase "central sensitization."

Durability of LTP in Cortex and in Spinal Dorsal Horn

In their review, Latrémolière and Woolf suggest that LTP in the cerebral cortex and in the spinal cord would be fundamentally different and this would also include the durability of synaptic plasticity: "That the activity-dependent synaptic plasticity in the dorsal horn responsible for central sensitization is reversible differs from the permanent activity-dependent synaptic change in the cortex."[11]

There are no studies demonstrating any fundamental difference in the durability of LTP at cortical versus spinal synapses. Activity-dependent potentiation at synapses in the hippocampus as well as in the superficial spinal dorsal horn both fulfill the criterion for LTP as they persist for at least 30 minutes. The durability of LTP depends on a number of variables including the induction protocol and the type of preparation.[16,20] In fact, the maximal duration of LTP at most synapses studied so far is unknown. This is also the case for LTP at synapses between primary afferent C-fibres and second order neurons in superficial spinal dorsal horn. Previous studies have shown that LTP at C-fibre synapses does not diminish within the recording periods.[7,8,12,17,22,23] It has never been claimed that any increase in synaptic strength must be irreversible to be labelled "LTP." Any irreversible change in synaptic strength would, by the way, severely impair the ability of the nervous system to adapt its functions to novel conditions. An irreversible change in synaptic strength is under physiological conditions most likely the exception rather than the rule.[20] Statements on different durability of synaptic plasticity in hippocampus versus spinal cord are presently not warranted by published data.

Input Specificity of LTP

The authors also comment on differences in the input specificity of LTP in the cortex versus LTP in the spinal cord and argue that "central sensitization" would involve a heterosynaptic LTP and "sensitization of the entire neuron."

"the major synaptic alteration underlying activity-dependent central sensitization is heterosynaptic potentiation, in which activity in 1 set of synapses enhances activity in nonactivated synapses, typically by 'sensitizing' the entire neuron,"[11] and "heterosynaptic facilitation alone is responsible for secondary hyperalgesia and allodynia."[11]

At present, nothing can be said about the homo- or heterosynaptic nature of LTP at spinal synapses of primary afferents, simply because this has not yet been studied. Likewise, it has never been shown that all synapses converging onto nociceptive neurons get "sensitized." Such a global increase in synaptic strength of virtually all synapses converging onto a neuron is called synaptic scaling.[13,19] Evidence for global changes of synaptic strength has been demonstrated for neurons in the brain but not for nociceptive neurons in the spinal dorsal horn.

At some regions in the brain, LTP is indeed probably homosynaptic in nature. As correctly

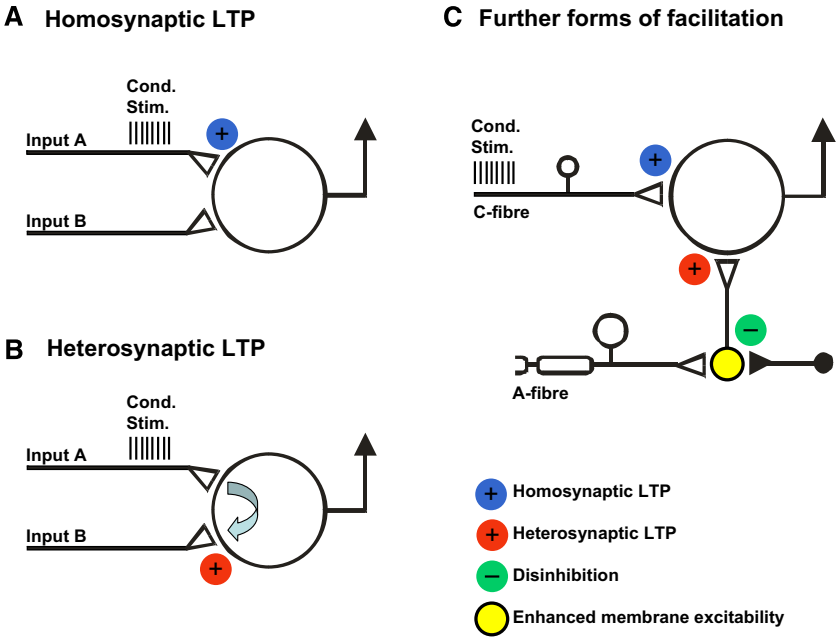

Figure 1. Fundamental differences between **(a)** homo- and **(b)** heterosynaptic plasticity versus other forms of facilitation. **(c)** Facilitation of A-fibre-evoked response by enhanced membrane excitability of an intercalated neuron, by disinhibition or by heterosynaptic potentiation.

stated in the review, homosynaptic LTP implies that the conditioning stimulus (eg, high- or low-frequency stimulation of some afferent nerve fibres converging onto the same neuron) leads to a potentiation of synaptic strength only at those synapses that were activated by the conditioning stimulus (Input A in Fig 1*a*), while the strength at other synapses remains unaltered (Input B in Fig 1*a*). Both forms of potentiation—homo- and heterosynaptic LTP—[1,4,9,15] have been identified at synapses in the brain.

Previous studies have demonstrated that conditioning stimulation of primary afferent C-fibres may enhance responses to A-fibre input. This does not, however, necessarily indicate the involvement of any heterosynaptic potentiation or synaptic scaling. A-fibre responses may be facilitated without any change in synaptic strength, eg, when an interneuron is intercalated (as shown in Fig 1*c*). Then, enhanced membrane excitability of the intercalated neuron,[10] or disinhibition[2,18,21] may equally well lead to enhanced A-fibre responses. Furthermore, conversion from inhibition to excitation anywhere along the pain pathways may also lead to exaggerated responses to A-fibre stimuli.[3,5,6] Thus, at present, nothing can be said about any heterosynaptic potentiation or synaptic scaling in pain pathways and their potential role for secondary hyperalgesia or mechanical allodynia. This is, however, a highly interesting topic for future studies.

"Central Sensitization" Versus LTP

Latrémolière and Woolf suggest not using the technical term "LTP" for long-term potentiation at synapses in the spinal cord:

"Perhaps, therefore, to avoid confusion with cortical plasticity, the term LTP should be avoided for homosynaptic potentiation in the spinal cord."[11]

In the scientific literature, any long-lasting increase in synaptic strength that is rapidly induced and persists for at least 30 minutes after termination of the conditioning stimulus is labelled "LTP." LTP may be ". . . expressed at possibly every excitatory synapse in the mammalian brain."[14] Why should it be confusing to use the same technical term for the long-term potentiation that has been identified at synapses of C-fibre afferents? I certainly suggest that in any scientific communication the same type of phenomenon or mechanism should always be given the same, unequivocal technical term. This naturally also applies to LTP independent of the location of the synapses involved (ie, in the cortex, the spinal cord or elsewhere in the nervous system), the type of synapse (excitatory or inhibitory), or the type of potentiation (eg, homo- or heterosynaptic). It would be rather confusing and at odds with the scientific literature on synaptic plasticity if we labelled the persistent increase in synaptic strength "LTP" anywhere in the nervous system but "central sensitization" in the dorsal horn.

Concluding Remarks

LTP at spinal synapses of C-fibres and LTP in hippocampus share induction protocols, pharmacology, signalling pathways, and mechanisms of maintenance. LTP should thus be used in each case as the proper technical term.

Primary hyperalgesia is an important clinical problem and much progress has been made in understanding its peripheral mechanisms. We and others suggest that, in addition, LTP at synapses of C-fibres also contributes to activity-dependent forms of hyperalgesia[17] and opioid-induced hyperalgesia.[7] Peripheral and spinal amplifiers of nociceptive activity likely act in concert to yield clinically relevant hyperalgesia and can both be targeted for an effective and safe therapy of pain.

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