Pregabalin inhibition of the excitatory transmission in the nociceptive amygdala of the mice with inflammatory pain

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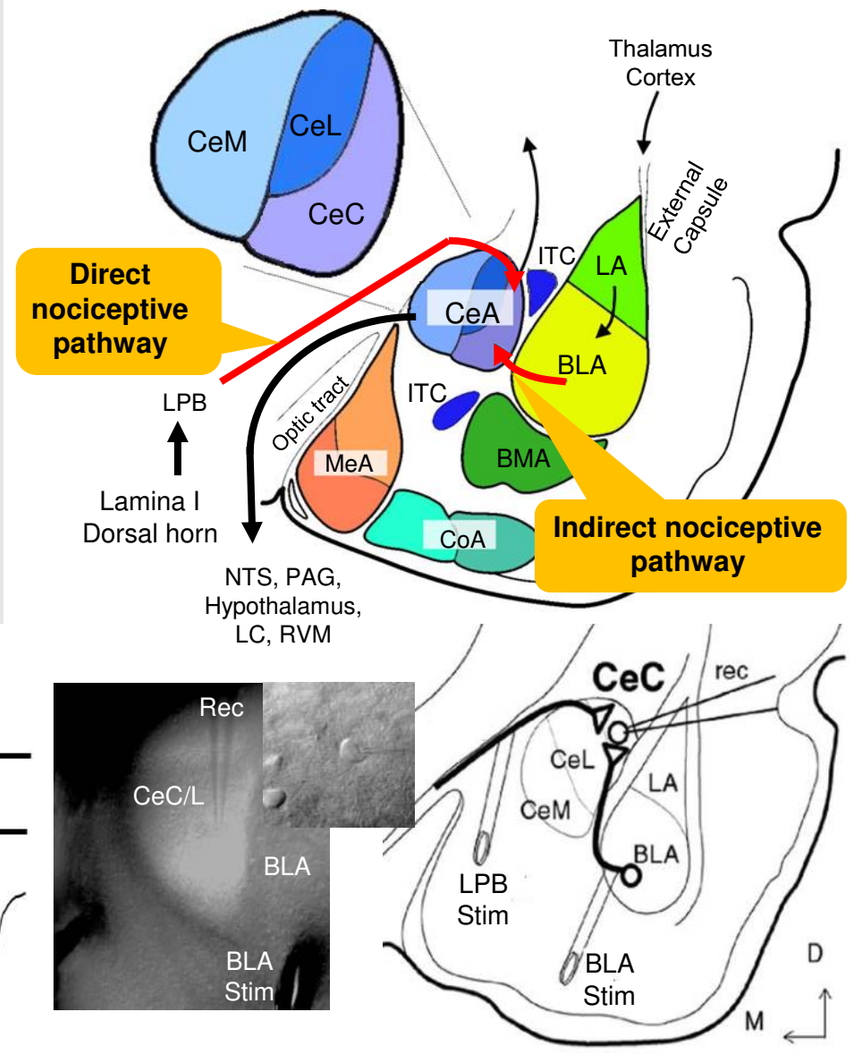
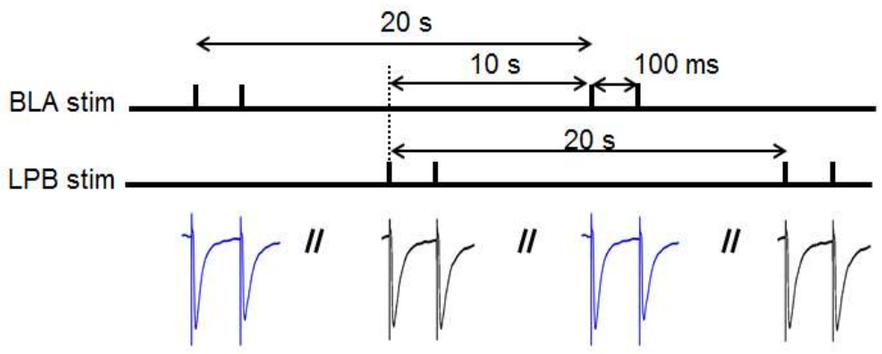
Introduction

Pregabalin (PGB), a widely used centrally acting analgesics for intractable chronic pain, is a ligand binding to the α2δ subunit of voltage-gated calcium channels which are widely expressed in the central nervous system. However, its site and mode of action remain largely undetermined. The amygdala is a kernel site for the enhanced nociception-emotion link in the chronic pain and also is rich in PGB binding sites. As the nociceptive information is conveyed to the amygdala via the thalamocortical pathway targeting the basolateral amygdala (BLA) and via the spinoparabrachial pathway targeting the central amygdala (CeA), it is of interest how PGB affects inputs from these distinct pathways converging to the output nucleus of the CeA. We have already reported that PGB inhibits the excitatory synaptic transmission at BLA-CeA synapses only in inflammatory conditions[1)]. We compared the effects of PGB on the converging excitatory inputs to CeA neurons between those from the BLA and those from the lateral parabrachial nucleus (LPB) by recording the postsynaptic currents in single CeA neurons.



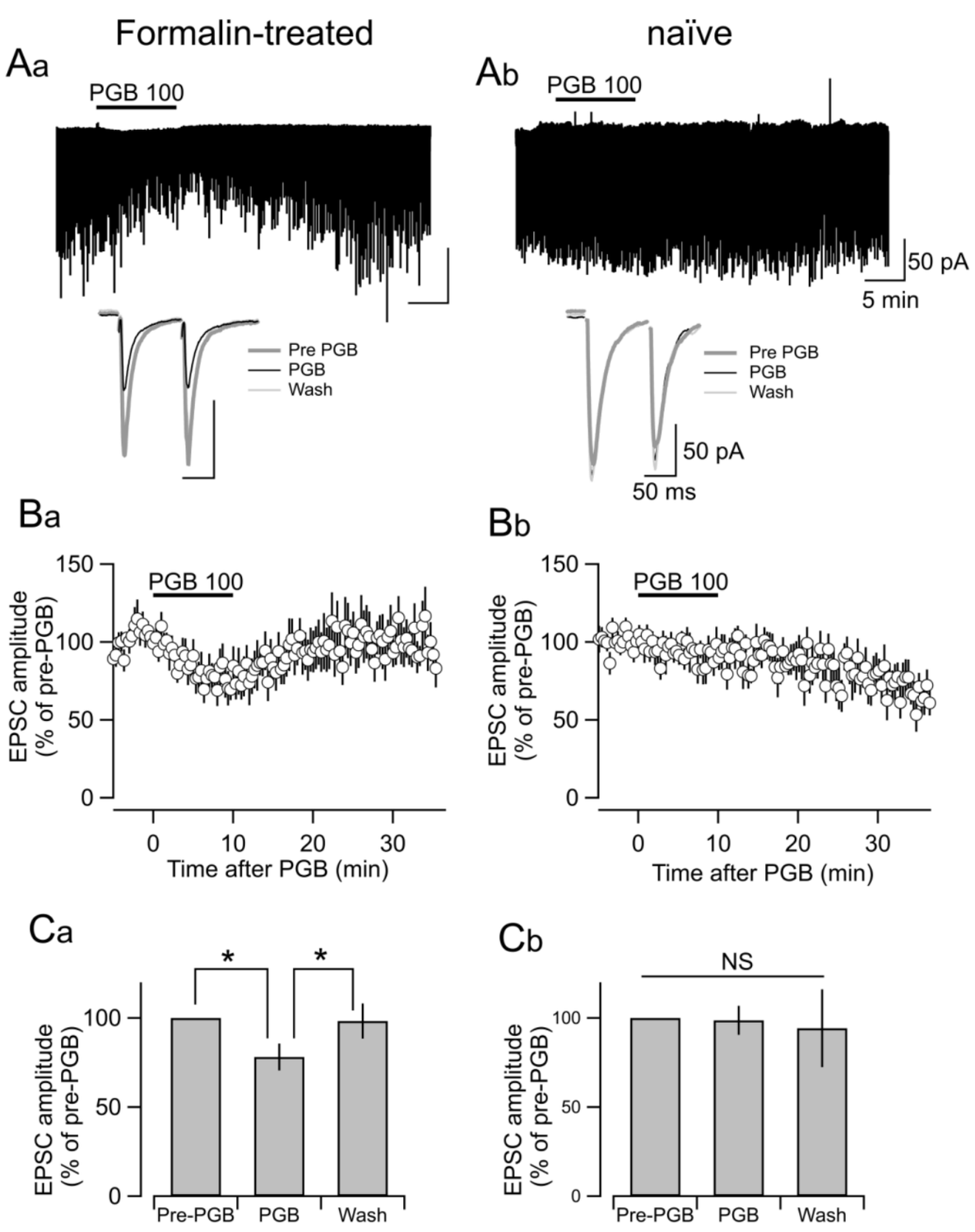
Methods

C57BL/6 mice (3-8 weeks-old) were used. Inflammation was induced by injecting 20 μL of 5% formalin into the intraplantar surface of the left hind paw. Acute coronal brain slices were prepared 8 hours post-injection. The stimulation electrodes were placed 1) on the fiber tract arising from the LPB and 2) within the BLA. These pathways were alternately stimulated. Excitatory postsynaptic currents in response to stimulation of LPB pathway ($EPSC_{LPB}$) and BLA ($EPSC_{BLA}$) were recorded from single neurons in the CeA using whole-cell patch-clamp technique. PGB (100 μM) was added to external solution and applied in the bath. Ten cells were analyzed. Wilcoxon signed-rank test were used to compare results. All data are presented by the mean ± SEM.

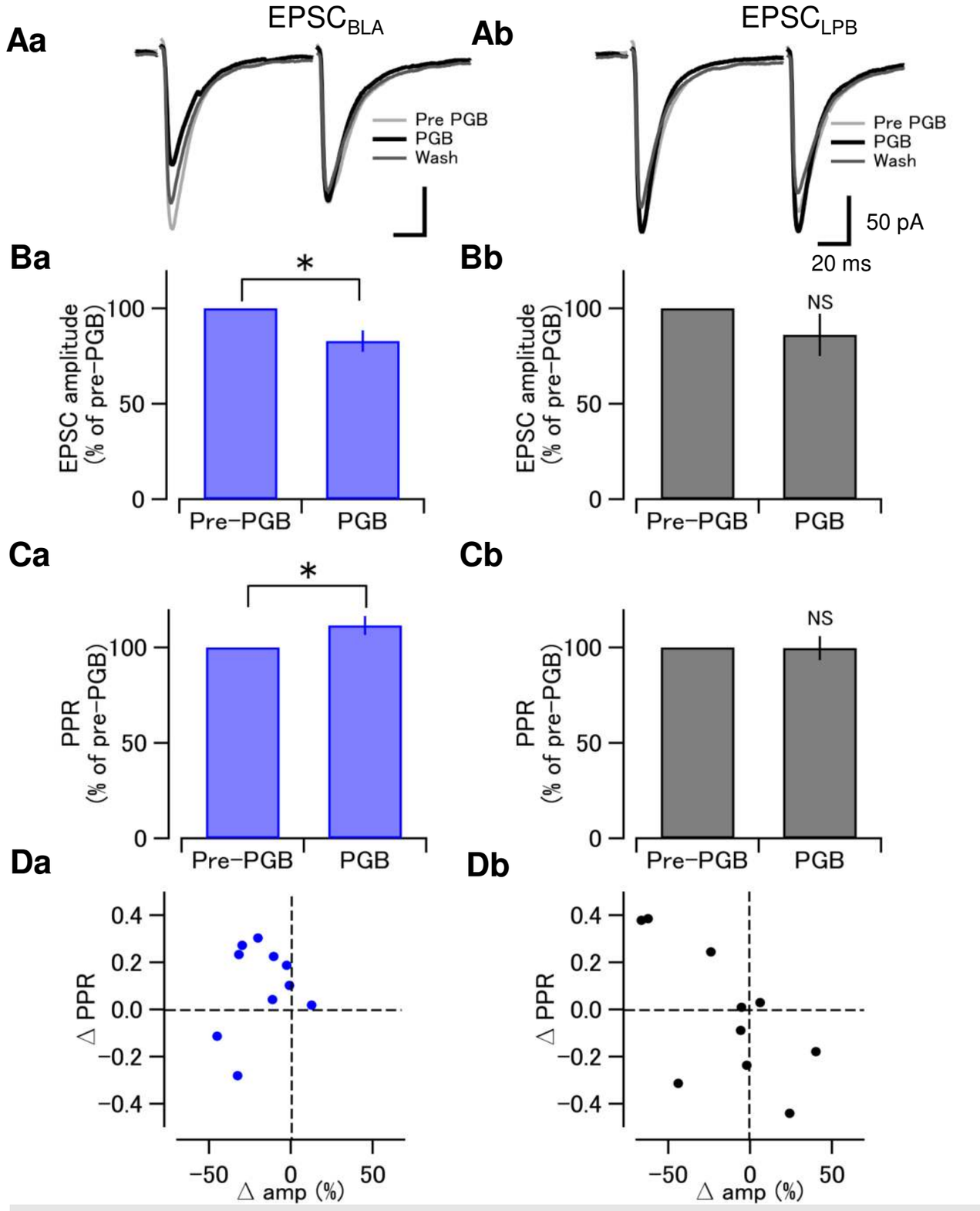


Results

PGB inhibits excitatory transmission from the BLA to CeA only in inflammation conditions



PGB inhibits excitatory transmission from the BLA to the CeA partly through reducing release probability but not at the LPB to CeA pathway



Discussion

- PGB inhibits excitatory transmission from the BLA to the CeA but not that from the LPB to the CeA pathway in the formalin injected inflammatory pain model mice.
- This decrease in the $EPSC_{BLA}$ amplitude by PGB was accompanied by a significant increase in paired pulse ratio, suggesting a presynaptic inhibition.
- PGB reduces neurotransmitter release by affecting release machinery.
- PGB might decrease central sensitization, thus mitigate chronic neuropathic pain symptoms.
- These results suggest that mode and mechanism of PGB effects differ between inputs of 'direct' (LPB origin) and 'indirect' (BLA origin), and more effective on the indirect pathway

Conclusions

PGB inhibits the BLA to CeA transmission through mechanism involving reduced release probability, particularly in inflammation conditions. Such pathway-dependence might partly defines the spectrum of PGB in treating the cognito-affective aspect of pain.

Reference

1) Yamamoto S et al. IASP 2016.

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Conflict of Interest: No potential COI to disclose