

GABA_B potentiator CGP7930 enhanced the effects of baclofen in rat hippocampal CA1 area

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CGP7930 is a recently discovered positive allosteric modulator of the GABA_B receptors; its effects on synaptic transmission in different brain areas still await evaluation. Using rat hippocampal slices, we aim to examine the effect of CGP7930 on CA1 synaptic transmission and on baclofen-induced modulation of CA1 synaptic transmission. fEPSPs and population spikes (PS) were evoked by the stimulation of the glutamatergic Schaffer collateral-CA1 synapses and recorded simultaneously in stratum radiatum and stratum pyramidale, respectively, using a multi-electrode recording system (MED64).

CGP7930 at 30 μM had no effect on fEPSP or PS with a paired-pulse paradigm (15ms paired-pulse interval). GABA_B antagonist CGP55845 also had no effect, indicating a low tonic level of GABA_B-mediated activity in the slice. GABA_B agonist, baclofen, inhibited both fEPSP and PS in a concentration-dependent manner. Moreover, the paired-pulse inhibition (PPI) of the PS, due to the activation of the GABA_A receptor-mediated bi-synaptic inhibitory pathway, was shown more sensitive to baclofen and was significantly reduced by a lower concentration of baclofen. More importantly, CGP7930 significantly potentiated baclofen-induced modulation of the PPI of the PS, without any significant effects on baclofen-induced inhibition of fEPSP or PS.

The results, therefore, show that baclofen differentially modulated GABA_A-mediated or glutamate-mediated synaptic transmission, which suggests pharmacologically distinct GABA_B receptors, located at different synaptic pathways in the rat hippocampal CA1 area. CGP7930 is also shown to differentiate the two types of GABA_B receptors. This GABA_B potentiator is shown to preferentially enhance the baclofen-induced modulation of the GABA_A-mediated synaptic inhibition recorded as the PPI of the PS, by an allosteric mechanism without any apparent agonist effects. The baclofen-induced inhibition of the glutamatergic synaptic responses, the fEPSP or the PS, was, however, not significantly affected by CGP7930.