Dihydropyridines as subunit-specific pharmacological probes of recombinantly expressed glycine receptors

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Glycine receptor (GlyR) chloride channels mediate inhibitory neurotransmission in the central nervous system. As GlyRs containing the α3 subunit are down-regulated during spinal inflammatory (PGE_2-mediated) pain sensitization, α3 subunit-specific potentiating drugs may hold promise as analgesic lead compounds. In addition, α3 subunit-specific inhibitors may provide useful tools for examining the physiological roles of this subunit. Nifedipine (NF) and nicardipine (NC), two derivatives of 1,4-dihydropyridine, are known as calcium channel blockers and have been used for treatment of hypertension. A previous study on rat spinal neurons indicated a direct interaction between NC/NF and GlyRs, although the composition of these receptors was unknown. Accordingly, the current study investigated the effects of NF and NC on α1 and α3 GlyRs. Both GlyRs were recombinantly expressed in HEK293 cells and currents were recorded by whole-cell patch clamp recording. It was found that the current response to glycine was modulated by NC in a voltage-independent manner. NC exhibited dual effects on the α1 GlyR. At concentrations between 0.1 and 100μM, NC enhanced the current response to low glycine concentrations (EC_{20-30}) with the maximal potentiation found at 30μM NC. No potentiation was found for α3 GlyRs when corresponding EC_{20-30} concentrations of glycine were applied whereas NC inhibitory potency was similar to the α1 GlyR. Although the effects of NF were also independent of voltage and glycine concentration, NF produced inhibition only at both receptors. The α1 GlyR was found to be more sensitive than the α3 GlyR to inhibition by NF. The subunit-specific effects of NF and NC may prove useful for differentiating α1 and α3 subunit-containing GlyRs in physiological experiments, and could provide leads to identifying the molecular determinants of their actions.