Supplementary information S4 | Molecular modelling of migraine

Systemic administration of nitroglycerin to human patients evokes an immediate aspecific headache, most probably as a result of the direct hypotensive effect of its product nitric oxide, mediated via its action on soluble guanylyl cyclase, increasing the formation of cyclic GMP (cGMP)\(^1\). The administration of nitroglycerin to migraineurs, however, promotes an additional delayed-onset migraine-type headache, indicating a central pathomechanism through which nitric oxide provokes hemicranial pain in susceptible subjects\(^2\). Indeed, cGMP levels have been found to be elevated in the rat brain peaking at 2 hours after systemic nitroglycerin administration\(^3\). Consistently, subcutaneous nitroglycerin induces the release of calcitonin gene-related peptide (CGRP) from the primary nociceptive trigeminal afferents\(^4\) and increases FOS expression in second-order neurons within the caudal trigeminal nucleus\(^5\), with the maximum at 4 hours after administration. In the same model, nitroglycerin triggers an increase in the number of neuronal nitric oxide synthase (nNOS)\(^6\) and calmodulin-dependent protein kinase II alpha (CamKIIalpha)\(^7\) expressing neurons in the CTN. These alterations indicate that, besides its peripheral vasodilating effect, nitric oxide probably contributes to migraine pathology via the activation of primary and subsequently secondary trigeminal nociceptive neurons, through nNOS-mediated self-amplification and CamKIIalpha-mediated phosphorylation of NMDA (\(N\)-methyl-D-aspartate) receptors. This knowledge provides preclinical approaches to examine the potential therapeutic value of putative anti-migraine compounds at specific end-points involved in the activatory cascade of trigeminal nociceptive system.