Prasugrel anti-ischemic effect in rats: Modulation of hippocampal SUMO2/3-IȻBŬ/Ubc9 and SIRT-1/miR-22 trajectories

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Abstract

The beneficial role of prasugrel, a P2Y12 receptor blocker, in several neurointerventional procedures has been reviewed clinically. Beyond its antiplatelet capacity, the potential neuroprotective mechanisms of prasugrel are poorly addressed experimentally. Relevant to the imbalance between neuro-inflammation and neuroprotective pathways in cerebral ischemia/reperfusion (I/R), our study evaluated the anti-ischemic potential of prasugrel treatment through tackling novel targets. Male Wistar rats were allocated into 2 sets; set 1 (I/R 60 min/3 days) to assess the neurological deficits/biochemical impact of prasugrel and set 2 (I/R 60 min/5 days) for evaluating short memory/morphological/immunoreactive changes. Each set comprised 4 groups designated as sham, sham + prasugrel, I/R, and I/R + prasugrel. Post-administration of prasugrel for 3 and 5 days reduced neurological deficit scores and improved the spontaneous activity/short term spatial memory using the Y-maze paradigm. On the molecular level, prasugrel turned off SUMO2/3-inhibitory kappa (Iə)BŬ, Ubc9 and nuclear factor kappa (NF-ə)B. Besides, it inhibited malondialdehyde (MDA) and inactivated astrocytes by downregulating the glial fibrillary acidic protein (GFAP) hippocampal immune-expression. Conversely, it activated its target molecule cAMP, protein kinase (PK)A, and cAMP response element-binding protein (CREB) to enhance the brain-derived nuclear factor (BDNF) hippocampal content. Additionally, cAMP/PKA axis increased the hippocampal content of deacetylator silent information regulator 1 (SIRT1) and the micro RNA (miR)-22 gene expression. The crosstalk between these paths partakes in preserving hippocampal cellularity. Accordingly, prasugrel, regardless inhibiting platelets activity, modulated other cellular components; viz., SUMO2/3-IəBŬ/Ubc9/NF-əB, cAMP/PKA related trajectories, CREB/BDNF and SIRT1/miR-22 signaling, besides inhibiting GFAP and MDA to signify its anti-ischemic potential.

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