

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

Hanan Salah ,Asmaa A Gomaa, Dalaal M Abdallah, Azza S Awad, Ayman A Soubh

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 (I +B .Ubc9 and nuclear factor kappa (NF- +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-I B 1Ubc9/NF- B, cAMP/PKA related trajectories, CREB/BDNF and SIRT1/miR-22 signaling, besides inhibiting GFAP and MDA to signify its anti-ischemic potential.

Toxicology and Applied Pharmacology 2021, September