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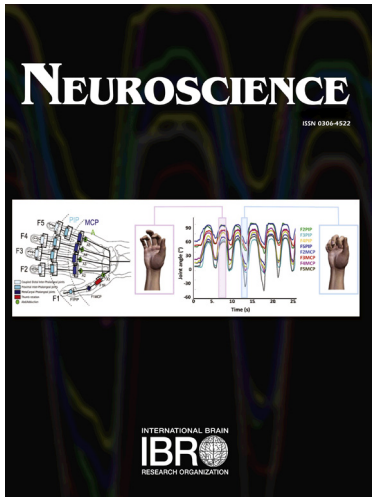


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Mohona Mukhopadhyay, Anurag singh, S Sachchidanand, Amal kanti Bera

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# Quercetin inhibits acid-sensing ion channels through a putative binding site in the central vestibular region

**MOHONA MUKHOPADHYAY,[a] ANURAG SINGH,[b] S SACHCHIDANAND [b] AND AMAL KANTI BERA[a] ***

[a] *Department of Biotechnology, Bhupat and Jyoti Mehta School of Biosciences Building, Indian Institute of Technology Madras, Chennai 600036, India*

[b] *National Institute of Pharmaceutical Education and Research (NIPER) Hajipur, Bihar, India*

*To whom correspondence should be addressed. E-mail: amal@iitm.ac.in; phone: 91-44-2257-4121; Fax: 91-44-2257-4102

**Abstract**

**Acid-sensing ion channels (ASICs) are associated with many pathophysiological processes, such as neuronal death during ischemic stroke, epileptic seizure and nociception. However, there is a dearth of ASIC-specific therapeutic blockers. Here we report that quercetin, a plant flavonoid, which is known for its neuroprotective effect, reversibly inhibits homomeric rat ASIC1a, ASIC2a and ASIC3 with an $IC_{50}$ of about 2 µM. Also, quercetin prevents low pH-induced intracellular calcium rise and cell death in HEK-293 cells, which have endogenous expression of ASIC1a and 2a. The inhibitory effect of quercetin on ASICs is not due to membrane perturbation, as it did not have any effect on other channels, like NMDA receptor, $GABA_A$ receptor and P2X4 receptor. Unlike quercetin, another flavonoid resveratrol had no effect on ASIC1a. Computational analysis revealed that quercetin binds to the channel in a cavity at the central vestibule, lined by several charged residues like Q276, R369, E373 and E416 in ASIC1a. Mutation of Arg369 to Ala or Glu416 to Gln abolished the**