Al collegio docenti del Dottorato in Medicina Molecolare

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Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels as target of new zetabradine derivatives and hydrogen sulfhyde (H_2S)

Introduction. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels mediate a Na^+/K^+ current (I_h) that is activated by hyperpolarization and regulated by intracellular cAMP/cGMP levels. HCN family comprises four homologous members (HCN1-4), differently expressed in the heart and the nervous system, where they control pacemaking and excitability. Because of this, HCN channels represent valuable targets to identify novel pharmacological molecules and endogenous mediators of potential interest to modulate their function or dysfunction in cardiac and neuronal models. This work aims to study the effect of PK19, a novel analogue of the I_h blocker zatebradine, and that of H_2S, an endogenous gasotrasmitter that modulates several ion channels, on HCN channels expressed in different experimental models in-vitro.
Methods. HEK293 cells expressing single HCN isoforms were cultured as previously described. Primary dorsal root ganglion (DRG) neurons were isolated from 3-week-old rats. Human atrial cardiomyocytes (hAMs) were isolated from patients undergoing cardiac surgery. PK19 and NaHS (H_2S donor) were tested on I_h by single-cell patch-clamp recordings.
Results. On HEK293 cells PK19 showed a preference toward HCN2/4 isoforms with respect to HCN1, being IC_{50} of I_h at physiological potential (-80mV) 0.32±0.08, 0.12±0.02 and 1.81±0.57 μM. In cultured DRG, 5μM PK19 reduced I_h at -80mV by 80% from 0.40±0.07 to 0.10±0.08. In hAMs NaHS showed a dose dependent double effect, increasing I_h at -80mV and at 10 and 100 μM concentrations from 0.33±0.08 to 0.45±0.11 and to 0.60±0.11, respectively, and decreasing it to 0.23±0.07 and to 0.25±0.06 at 1 and 5 μM, respectively.
Further experiments are necessary to refine data on PK19 in DRG neurons and assess whether H_2S interaction with HCN channels is direct or mediated by modifications of intracellular cAMP/cGMP levels. These findings may open novel perspectives to modulate I_h function and dysfunction in cardiac and nervous cells.

Participations at congresses and conferences

- Cardiac Bioelectricity & Arrhythmia Center (CBAC) Seminars Series, “Abnormalities in Sodium Current and Calcium Homeostasis as Drivers of Arrhythmogenesis in Hypetrophic Cardiomyopathy” by Elisabetta Cerbai. December 15 th, 2020
- Webinar “Vaccine Hesitancy Forum Covid-19” by Cianzia Caporale, Giovanni Maga, Giovanni Rezza, Andrea Grignolio, Vincenzo Baldo, Enrico Bucci, Anna Franca Cavaliere, Michele Cenversano, Vincenzo Crupi, Paolo F. D’Ancona, Antonio Ferro, Daniel Fiacchini, Teresa Gavaruzzi, Roberto Ieraci, Giuseppe Ippolito, Pierluigi Lopalco, Matteo Motterlini, Anna Odone, Antonella Viola, Stanley A. Plotkin. January 8 th, 2021
- Webinar Central European Time entitled “Control of Ca2+ in the heart: free and beyond” by David Eisner. January 14th, 2021
- EuroCVP 2021, the Annual Meeting of ESC Working Group on Cardiovascular Pharmacotherapy”. June 10th - 12th, 2021
- Minisimposio “Sperimentazione animale in biomedicina – Un percorso di scienza, storia, diritto , etica e medicina, il cervello tra Homo sapiens e primate non-umani: sviluppo, evoluzione e potenzialità”. June 21th, 2021
- Seminario “Neurofisiopatologia del dolore neuropatico" tenuto dal Dott. Lorenzo Di Cesare Mannelli, Dipartimento di NEUROFARBA, Università degli studi di Firenze. July 9th, 2021
- Seminario “Neurofisiopatologia del dolore viscerale" tenuto dalla Dott.ssa Elena Lucarini, Department of NEUROFARBA, University of the Study of Florence. July 16th, 2021

Publications

1. Balducci V, Cerbai E. Toward an in vitro human pacemaker. Pflugers Arch. 2021 Jul;473(7):989-990. doi: 10.1007/s00424-021-02585-4.
2. Balducci V, Credi C, Sacconi L, Romanelli MN, Sartiani L, Cerbai E. The HCN channel as a pharmacological target: Why, where, and how to block it. Prog Biophys Mol Biol. 2021 Jul 22:S0079-6107(21)00092-4. doi: 10.1016/j.pbiomolbio.2021.07.010.
3. Balducci V, Faris P, Balbi C, Costa A, Negri S, Rosti V, Bollini S, Moccia F. The human amniotic fluid stem cell secretome triggers intracellular Ca^{2+} oscillations, NF-κB nuclear translocation and tube formation in human endothelial colony-forming cells. J Cell Mol Med. 2021 Aug;25(16):8074-8086. doi: 10.1111/jcmm.16739.
4. Credi C*, Balducci V*, Munagala U, Cianca C, Bigiarini S, de Vries AAF, Loew LM, Pavone FS, Cerbai E, Sartiani L, Sacconi L. Fast Optical Investigation of Cardiac Electrophysiology by Parallel Detection in Multiwell Plates. Front. Physiol. 2021 Sept;12:692496. doi: 10.3389/fphys.2021.692496.