No. 1547

Novel Na^+ and K^+ Channel Mutations Responsible for Human Cardiac Sudden Death

Tomoe Nishitani[1], Shigeo Wakabayashi[1], William A. Coetzee[2]

[1]Department of Molecular Physiology, National Cardiovascular Center Research Institute
[2]New York University, Langone Medical Center, Departments of Pediatrics

Summary

Sudden infant death syndrome (SIDS), defined as the death of an individual before his or her first birthday, is a major concern in the world. In Japan, the infant mortality rate is 1 death per 6000-7000 live birth. One of the mechanisms underlying SIDS is various mutations in ion channels, because ion channels determine action potential shape, intracellular Ca^{2+} influx/efflux and contractility, thus mutation of ion channels is often responsible for cardiac arrhythmia. By collaboration with the New York City Office of the Chief Medical Examiner, we discovered genetic variation in the SCN5A gene, coding for the Nav1.5 Na^+ channel, to be associated with a case of SIDS of a five month-old girl who died suddenly in her sleep. Two point mutations occurred at the C terminus of SCN5A gene (mutation A and mutation B). Mutation B results in introduction of a premature stop codon and truncation of the C-terminus. We examined the effects of these mutations when expressed in HEK293 cells, individually or combined, on Nav1.5 channel function and trafficking. The mutation A drastically reduced the Na^+ channel current density (~ 44% of wild type) and slowed the Na^+ current inactivation rate. On the other hand, the mutation B and double mutation had negligible effects. None of the mutations affected the voltage dependence of steady-state activation and inactivation or influenced the late Na^+ current or the recovery from inactivation. Our data with biochemical and immunofluorescent approaches demonstrated that the mutation A decrease the amount of Na^+ channel protein at the plasma membrane without changing them in whole cells. These results suggest that mutation A caused trafficking defects rather than transcription or translation defects, or enhancement of degradation. Taken together, these data demonstrate that mutation A was sufficient to produce a severely dysfunctional Nav1.5 channel, which likely is a major contributing factor to the sudden death of this SIDS victim.