N-type calcium channel blockade: a new approach to preventing sudden cardiac death?

Stanley Nattel*

Department of Medicine and Research Center, Montreal Heart Institute and Université de Montréal, 5000 Belanger Street E, Montreal, QC, Canada H1T 1C8

Online publish-ahead-of-print 21 August 2014

This editorial refers to ‘Inhibition of N-type Ca\(^{2+}\) channels ameliorates an imbalance in cardiac autonomic nerve activity and prevents lethal arrhythmias in mice with heart failure’ by Y. Yamada et al., pp. 183–193, this issue.

Congestive heart failure (CHF) is a major cause of death in the population, and sudden cardiac death (SCD) is a common terminal event in CHF. CHF patients have elevated resting sympathetically mediated activity, and a simple carbohydrate meal can further raise their sympathetic nerve discharge rates to values characteristic of patients with acute myocardial infarction. Autonomic abnormalities play important roles in SCD due to ventricular tachyarrhythmias (VTs) resulting from a wide range of cardiac pathologies, including ischaemic heart disease, CHF, and genetic CHF syndromes. Classical antiarrhythmic drugs are ineffective in preventing CHF-associated SCD, whereas beta-adrenoceptor antagonists have significant value, emphasizing the importance of the autonomic nervous system in VTs related to CHF.

A wide range of voltage-dependent Ca\(^{2+}\) channels have been described, including L-type Ca\(^{2+}\) channels (LTCCs) responsible for cardiac excitation–contraction coupling, T-type Ca\(^{2+}\) channels (TTCCs) involved in cardiac automaticity, and N-type neuronal Ca\(^{2+}\) channels (NTCCs). NTCCs, encoded by Cav2.2 (CACNA1B) subunits, are particularly involved in cardiovascular sympathetic regulation.

1. Autonomic nervous system intervention in CHF-related SCD

In this issue of Cardiovascular Research, Yamada et al. report the results of a fascinating series of experiments that evaluate the role of NTCCs and their inhibition in a model of CHF-associated SCD. The model involves mice engineered to produce cardiomyocyte-specific overexpression of a dominant-negative (dn) form of neuron-restrictive silencing factor (NRSF), a transcriptional repressor that controls cardiac gene expression. Cardiac-restricted NRSF suppression induces a dilated cardiomyopathy with a high incidence of VTs, and sudden premature death presumably due to arrhythmias. Yamada et al. study the effects of a variety of interventions targeting the autonomic nervous system [including genetic NTCC suppression, a drug that inhibits NTCCs (cilnidipine) and beta-adrenoceptor blockade (bisoprolol)] on VTs and mortality.

Interestingly, all the anti-sympathetic interventions normalized indices of abnormal autonomic function (increased urinary noradrenaline secretion and reduced high- and low-frequency components of heart rate variability), suppressed VTs, and reduced mortality. There were some important differences in consequences among the interventions, however. Whereas bisoprolol and cilnidipine had no effect on cardiac function, genetic NTCC suppression (heterozygous Cav2.2 knockout) normalized left-ventricular dimensions and systolic function indices, indicating reversal of the dnNRSF-induced cardiomyopathy.

2. NTCC inhibition with cilnidipine as an anti-SCD intervention

Cilnidipine is a ‘fourth-generation’ Ca\(^{2+}\) channel blocker. Its dissociation constant (Kd) for NTCCs is at least an order of magnitude less than that of 9 other Ca\(^{2+}\) channel blockers, with a higher Kd for LTCC blockade than the other agents, giving it ≥20-fold increased selectivity for NTCCs at a constant test potential (−80 mV). Studies in well-controlled animal models suggest that the drug decreases sympathetic effects on the heart, with reduced heart rate and contractility. Clinical investigations have provided variable results, some compatible with reduced sympathetic outflow and others not so clear-cut.

In the Yamada study, cilnidipine produced dramatic protection against autonomic-tone abnormalities, VTs, and death in the dnNRSF mouse CHF model. If the drug could be shown to have similar effects in human CHF patients, it could be a very valuable component of SCD prevention in such individuals. At the very least, consideration should be given to a controlled clinical trial comparing the effects of cilnidipine with those of a more standard dihydropyridine drug like amlodipine on indices of autonomic function and ventricular ectopy in CHF patients. Positive results would motivate a larger scale study on ventricular arrhythmias and potentially lethal arrhythmias, perhaps beginning with a trial in high-risk subjects with implanted defibrillators.
3. Limitations of the study

Although the Yamada study is interesting and uses several elegant models, it has a number of significant limitations. First, there are important discrepancies between the effects of pharmacological autonomic inhibition and genetic NTCC inhibition. Cilnidipine- and bisoprolol-treated mice showed reduced arrhythmias and autonomic abnormalities, but the CHF phenotype remained unabated, whereas the CACNA1B heterozygous knockout mice demonstrated reversal of autonomic, arrhythmic, and haemodynamic abnormalities. The authors note the discrepancy for cilnidipine and suggest that it may be due to adverse effects of the drug’s LTCC blocking action on cardiac function, to insufficient cilnidipine doses, or to a lack of central nervous system penetration of cilnidipine. The authors do not comment on the discrepancy between the benefits of genetic NTCC inhibition against CHF and the lack of such benefit with bisoprolol.

Another internal inconsistency relates to the mortality rates of dnNRSF mice in the various experimental series. Bisoprolol-treated dnNRSF mice had a mortality rate of ~20% at 90 days. This was significantly lower than the mortality rate of the control dnNRSF group, >60% at 90 days (Figure 3N). However, the mortality of the latter group was unusually high, compared with virtually no mortality at 90 days (13 weeks) in the dnNRSF control group for the cilnidipine studies (Figure 1E) and a ~25% death rate for the dnNRSF/CACNA1B+/− mice in the genetic NTCC suppression study (Figure 6A). With a more typical control-group mortality, there would have been no significant difference with bisoprolol therapy; this discrepancy requires resolution.

Another concern relates to the functional selectivity of cilnidipine in vivo. The selectivity reported for NTCCs based on in vitro studies is indeed impressive.11,10 However, the Kd values were obtained in voltage-clamp studies at ~80 mV. Ca2+ channel blocking action is critically dependent on the frequency and voltage profile of action potential history; therefore, in vivo blocking effects are poorly predicted by in vitro blocking potentials under controlled conditions.11 The in vivo effects of ‘selective’ Ca2+ channel suppressing drugs may thus differ greatly from in vitro predictions or from the effects of truly specific genetic suppression. For example, quite a number of studies have shown protective effects of the TTCC-selective blocker, mibefradil, on ventricular remodelling post-myocardial infarction; however, TTCC knockout mice show worse ventricular function impairment and arrhythmogenesis post-myocardial infarction than wild-type mice.12 A final issue that remains to be resolved is the mechanism of death in dnNRSF mice. While the deaths appear to be sudden (mice found dead in their cage) and the mice clearly are prone to VTs, it remains to be clarified whether VTs are truly the cause of their premature death. Mice are resistant to ventricular fibrillation, and even in humans Holter monitor-recorded SCD is not infrequently caused by bradyarrhythmias.13 The authors do provide one example of a fatal VT in a nitrendipine-treated dnNRSF mouse (Supplemental Figure 2), but more detailed information on cardiac rhythms recorded by ambulatory monitoring at the time of death would be of interest.

4. Conclusions

The study by Yamada et al. provides plenty of food for thought. The important role of autonomic neural activity in cardiac arrhythmias, including VTs causing SCD, has long been recognized.1 The notion of suppressing arrhythmia risk by interfering with autonomic neural function through the manipulation of neuronal ion channels has not, to my knowledge, been proposed before. The ability of cilnidipine to fulfil this role certainly merits further examination. At worst, this will be another potentially interesting, but failed new antiarrhythmic drug approach. At best, it will introduce a new and valuable class of antiarrhythmic drug to a class of agents badly in need of rejuvenation.

Conflict of interest: none declared.

Funding

This work was supported by the Canadian Institutes of Health Research (grants 6957, 44365, and 68929) and the Heart and Stroke Foundation of Canada.

References