Letter to the Editor on NaV1.8

To the Editor:

The recent volume 111 of Circulation Research focuses on the SCN10A gene that encodes the TTX-resistant NaV1.8 current. Yang et al. demonstrate that NaV1.8 is the dominant carrier of the late sodium current that regulates cardiac action potential duration. They demonstrate the role of SCN10A with gene ablation and by use of the specific NaV1.8 blocker A-803467. A-803467 at 30 nmol/L entirely blocked the late sodium current in mouse cardiomyocytes and in the ND7/23 cell line overexpressing NaV1.8. They show that NaV1.5 in the presence of 100 nmol/L ATX-II to remove inactivation produces a late sodium current that is insensitive to A-803467. Unfortunately, they do not test the effects of ATX-II on the NaV1.8 late current overexpressed in the ND7/23 cells or in cardiac myocytes. However, other groups have looked at the NaV1.8 current in small-diameter dorsal root ganglion neurons and have shown no effect with the addition of ATX-II. This means that using ATX-II to induce a late sodium current and a proarrhythmic state in cardiac cells is physiologically and pharmacologically inappropriate. Screening of antiarrhythmic compounds in overexpressing NaV1.5 cells or cardiac cells treated with ATX-II may well lead to false-positive/false-negative hits because the physiological target for the late sodium current is NaV1.8. In addition, drug discovery pain programs targeting NaV1.8 in dorsal root ganglion neurons will now need to test their compounds for cardiac side effects. It will be important to evaluate the identity of the late sodium current in adult human cardiac cells and the role of NaV1.8 and A-803467 on the human cardiac action potential.

Disclosures

None.

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References

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