The HCN Ion Channel Blocker Ivabradine As An Analgesic In Inflammatory And Neuropathic Pain

Ayesha Sengupta, Gareth Young, Elizabeth Mooney, Edward Emery, Peter McNaughton

University of Cambridge, Cambridge, UK

Background and Purpose:

Inflammatory and neuropathic pain conditions represent an unmet clinical need as current therapies are associated with unpleasant side-effects and, in the case of neuropathic pain, have limited efficacy. The HCN2 ion channel has been identified as a key downstream target in the cellular events associated with pain (Emery et al., 2011), suggesting that blocking HCN2 ion channels could alleviate pathological pain. Here, we investigated whether the HCN channel blocker ivabradine, currently used as a bradycardic agent, also has efficacy as an analgesic. We tested ivabradine both in patch-clamp experiments and using in vivo pain models, and we compared its analgesic action to the bradycardia it caused.

Experimental Approach:

Whole-cell patch clamp electrophysiology was used to measure I_h current block by ivabradine in mouse DRG neurons (Emery et al, 2011). The effect of ivabradine, gabapentin and saline were assessed in two mouse models of pain: a model of inflammatory pain (the formalin test, Tjolsen et al., 1992) and a model of neuropathy (chronic constriction injury, CCI, Bennett and Xie, 1988). The bradycardic effects of ivabradine, governed primarily by block of HCN4, were monitored with pulse oximetry. Gross motor side effects of ivabradine and gabapentin were assessed using the rotarod test.

Key Results:

At 30µM, ivabradine blocked 99.9 +/- 0.02 % (n = 9) of I_h in vitro 300s after drug application. Both gabapentin, a drug currently used to treat neuropathic pain, and ivabradine had analgesic effects in neuropathic pain (t-test; 7 days after CCI, gabapentin [n=9]: p=0.0002, ivabradine [n=10]: p=0.0007, saline [n=11]: p=0.6007). Ivabradine reduced pain responses in the second phase of the formalin test (t-test; 5mg/kg ivabradine [n=6] compared to saline [n=12]: p=0.0054). Ivabradine had bradycardic effects at its analgesic doses for inflammatory pain (IC_{50} of ivabradine for heart rate: 3.4mg/kg [n=30], IC_{50} of ivabradine for inflammatory pain [n=36]: 2mg/kg).

Unlike gabapentin, ivabradine did not cause general motor deficits, measured from the time spent on rotarod, at analgesic doses (t-test; 30 minutes post-drug, gabapentin [n=5] vs. saline [n=5]: p=0.0138, ivabradine [n=5] vs. saline [n=5]: p=0.9194).

Conclusions and Implications:
The HCN channel blocker ivabradine is an efficacious analgesic in mouse models of neuropathic pain, but was shown to cause bradycardia at analgesic doses. HCN channel blockers appear to have fewer sedative side effects than gabapentin, a widely used treatment for neuropathic pain.