NO donors increase persistent sodium current in HEK293 cells transfected with the human cardiac Na^+ channel α-subunit

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Voltage-gated Na^+ channels play an essential role in excitable cells in which they transiently increase Na^+ conductance in response to membrane depolarisation. However, many tissues have a component of Na^+ current that is resistant to inactivation. This persistent Na^+ current (I_{Nap}) plays an important role in generation of rhythmic oscillations in neurons. Pathological changes in these channels are associated with diseases such as ischaemia, cardiac arrhythmias and epilepsy. Nitric oxide (NO), the major endothelium-derived relaxing factor, reduces whole-cell Na^+ current in isolated ventricular myocytes (Ahmmed *et al.*, 2001) but increases I_{Nap} in rat neuronal and cardiac cells (Hammarstrom & Gage, 1999). NO is also a potential endogenous regulator of I_{Nap} under physiological and pathophysiological conditions (Ahern *et al.*, 2000). The target for NO on Na^+ channels is not known.

We have tested the effects of NO on I_{Nap} in HEK 293 cells transiently transfected with the human cardiac Na^+ channel α-subunit. Persistent Na^+ channel activity in inside-out patches was increased ~10 fold after exposure to NO donors, s-nitroso-n-acetyl penicillamine (SNAP) and sodium-nitroprusside (SNP). Our results suggest that the effect of NO on I_{Nap} is caused by NO directly interacting with Na^+ channel α-subunit, or with closely associated protein(s): Na^+ channel β-subunits appear not to be necessary for this effect. The effect of NO on I_{Nap} was inhibited by the sodium channel blocker, lidocaine (50 μM) and by the reducing agent dithiothreitol (DTT, 2 mM).

Ahern, G. P., Hsu, S. F., Klyachko, V. A. & Jackson, M. B. (2000) *Journal of Biological Chemistry,* **275,** 28810-28815.

Ahmmed, G. U., Xu, Y., Hong Dong, P., Zhang, Z., Eiserich, J. & Chiamvimonvat, N. (2001) *Circulation Research,* **89,** 1005-1013.

Hammarstrom, A. K. M. & Gage, P. W. (1999) *Journal of Physiology,* **520,** 451-461.