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Characterisation of the Cold-Sensitivity of the Sympathetic Nervous System

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***Introduction*:** Body temperature regulation is controlled by the sympathetic nervous system. Mouse sympathetic neurons have been shown to be activated by cold, but the mechanism remains unclear. In contrast, the somatosensory nervous system uses transient receptor potential (TRP) channels to sense temperature. The menthol-sensitive TRPM8 ion channel is its main cold sensor, but it is not expressed in the sympathetic nervous system[1]. Similarly, TRPA1 is expressed in less than 4% of SCG neurons, which is too few to account for the observed cold sensitivity[2]. Therefore, there must be another mechanism.

Cooling of mouse sympathetic neurons *in vitro* causes an intracellular calcium increase that is not accompanied by any detectable ionic current. We hypothesized that this cold response may be mediated by a leak from voltage-gated calcium channels (VGCC), or activation of the STIM/Orai system for calcium entry, which is normally responsible for replenishing intracellular calcium stores.

***Method*:** C57/Bl6J mouse superior cervical ganglia (SCG) were removed, dissociated using *papain* and *collagenase IV* enzymes, and cultured on glass coverslips for one day before use. Intracellular calcium levels were measured *in vitro* in these sympathetic neurons using ratiometric calcium imaging. Neurons were perfused with cold solution (5℃) to evoke responses in the absence and presence of various drugs.

***Results*:** Cold-responses were abolished in the absence of extracellular calcium, and upon application of the calcium-entry blocking ion *Cd2+* (100 µM). The following drugs caused a small (30%) reduction of cold-sensitivity: L-type VGCC blockers *nifedipine* (5 µm) or *verapamil (100 µM)*, T-type VGCC blocker *mibefradil (10 µM)*, non-selective VGCC blocker *bepridil* (10 µM). Orai1/2 channel blocker *YM58483* (3 µM) caused a much larger (70%) reduction in cold-sensivity. Gd^{3+}, which blocks both VGCC and Orai channels completely abolished cold-sensitivity.

***Conclusion*:** Calcium enters through the plasma membrane upon cooling of sympathetic neurons. This mechanism seems to be mediated in part by voltage gated calcium channels (VGCC), but mainly by the STIM/Orai system for calcium entry.

***References*:**

1. Smith MP et al. (2004). NeuroReport 15(9): 1399-1403.

2. Munns C et al. (2007). Cell Calcium 41: 331-342.