CROSSTALK

Rebuttal from Raj K Goyal

Raj K Goyal
Harvard Medical School and VA Boston Healthcare System, West Roxbury, MA 02132, USA

Email: raj_goyal@hms.harvard.edu

Proposed models of involvement of interstitial cells of Cajal (ICC) in neuromuscular transmission (NMT) include mandatory, optional, or complementary (Goyal, 2016). However, the data on which these models are based are incompatible with each other. Sanders *et al.* (2016) do not specifically identify the model they support and as such make their view of the specific role of ICC in NMT difficult to understand.

A mandatory role of intramuscular ICC (ICC-IM) was suggested by the finding of loss of nitrergic inhibitory junction potential (IJP) in the ICC-deficient W/W^{v} mouse (Sanders *et al.* 2016). However, because of failure to reproduce the finding, the view of the mandatory role of ICC in nitrergic NMT is not supported (Goyal, 2016).

Later, it was found that nitrergic NMT also remained intact in animals with conditional deletion of ICC (Klein *et al.* 2013). However, genetic deletion of Prkg1, a signalling molecule in the nitrergic signalling pathway, abolished nitrergic IJP. Klein *et al.* proposed that ICC also prevent accessibility of nitric oxide to smooth muscle. Thus, when present, ICC transduce nitrergic NMT, but when ICC are lacking, direct NMT takes place (Klein *et al.* 2013). Bhetwal *et al.* (2013) adopted this model for cholinergic NMT when the original finding of loss of cholinergic NMT in ICC-deficient W/W^{v} mice could not be reproduced (Ward *et al.* 2000; Goyal, 2013)

Most recently, Groneberg and colleagues reported that deletion of NO-sensitive G-cyclase (NO-GC) in both ICC and smooth muscle was necessary to block nitrergic NMT (Groneberg *et al.* 2013). This model supported both direct and ICC-transduced NMT. Demonstration of active generation of nitrergic inhibitory junction potentials in the smooth muscle provided proof for the existence of direct NMT (He & Goyal, 2012). However, the involvement of ICC in NMT remains hypothetical because of the lack of validation of cell-specific deletions (Groneberg *et al.* 2013) and the presence of functional gap junctions between the ICC and smooth muscles (Sibaev *et al.* 2006; Lies *et al.* 2014). In any case, Sanders *et al.* (2016) should clearly state which of the specific roles of ICC in NMT they currently support.

ICC are not implicated in transducing signals of neurotransmitters other than NO to smooth muscle. PDGFRα^{+} fibroblasts may transduce purinergic inhibitory NMT (Sanders *et al.* 2016). However, it is unlikely that different interstitial cells are involved in different types of NMT. Direct NMT provides a unifying mechanism of all NMT.

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Additional information

Competing interests

None declared.

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