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Thermal Gradient Ring reveals temperature-dependent phenotypes of diabetic neuropathy in mice

Aim: Diabetic peripheral neuropathy (DPN) includes symptoms of thermosensory dysfunction. The authors used STZ mice [that did not exhibit change in transient receptor potential (TRP) ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) levels] and compared them with TRPV1/A1 knock out. They observed same hypoalgesia using Plantar test and a hot-plate test, which evaluate reflex behaviors by mice, but also avoidance behaviors upon detection of peripheral thermal nociceptive stimuli. These tests did not discriminate differences. They found that the behavioral assay called Thermal Gradient Ring clearly discriminated temperature-dependent phenotypes between the DPN and TRPV1$^{-/-}$ mice. They suggested this behavioral assay system analyze the DPN phenotypes more in detail.

*Methods***:** They treated WT mice C57BL6/NCr and two mice models TRPV1$^{-/-}$ and TRPA1$^{-/-}$ with STZ to induce type 1 diabetes (DM). They performed longitudinal studies using Plantar test and a hot-plate test and then evaluated calcium and gene expression in the dorsal root ganglia of mice. They also evaluated structural changes using transmission electronic microscopy. Lastly, they introduced a newly described test, the so-called Thermal Gradient Ring and proposed that this test can predict better temperature-dependent behavior between the different models.

*Results***:** Using a Plantar test and a hot-plate test they observed a gradual reduction of thermal sensitivity after administering STZ in mice and not hyperalgesia even with low thermal stimuli. For analysis, they used mice 5 weeks after STZ (10 weeks of age) showing significant thermal hypoalgesia. They performed Plantar test experiments using TRPV1$^{-/-}$ and TRPA1$^{-/-}$ mice treated with STZ and found no difference in paw withdrawal latency (PWL) in TRPV1$^{-/-}$ mice with and without DM, although the PWL in TRPV1$^{-/-}$ (non-DM) mice were significantly longer compared to WT (non-DM) mice even before the STZ treatment. In addition, the PWL of TRPA1$^{-/-}$ (non-DM) mice were similar as those of WT (non-DM) mice, but TRPA1$^{-/-}$ mice with DM exhibited similar results as WT (DM) mice. They suggested that TRPA1 is not involved in STZ-induced DPN. TRPV1 $^{-/-}$ did not exhibit PWL changes implying that TRPV1 is maybe not involved in DPN. They did not observe any significant difference in expression (mRNA or protein level) or function (Ca^{2+}-imaging), or structural damages in all models tested 5 weeks after STZ. They showed a significantly greater expression of TRPV1 at both mRNA and protein levels 2 weeks after STZ. Then, using the Thermal Gradient Ring test they observed differences between WT (non-DM) and WT (DM) mice (5 weeks after STZ); and they also observed that temperature preference was shifted to lower temperatures in mice with WT (DM) when compared to WT (non-DM) and TRPA1$^{-/-}$ (non-DM) mice. WT (DM) mice preferred lower temperatures than WT (non-DM) mice 5 weeks after STZ.

Conclusions: TRPV1 and TRPA1 could not be associated with thermosensory impairment in DPN. Avoidance and preference behavioral methods may better analyze the progression of DPN by response to thermal stimuli.

Comment. This paper is of interest because it highlights the fact that thermosensation is complex, multifactorial and that many models may exhibit similar hypoalgesia when using Plantar test but may have in fact different thermosensation phenotypes and mechanisms. It stresses the fact that more specific tests are needed, and the field may try the Thermal Gradient Ring to phenotype thermosensation of their animals. The authors also suggest with data (that are for some of them in contradiction with the literature) that TRPA/V channels are not involved in DPN. I would be careful with such conclusions since they use whole body KO that may show behavior due to developmental dysfunction for example. However, it is of interest to go back to this channel concept that are crucial to better understand the disease.

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Reference. Sasajima S, Kondo M, Ohno N, Ujisawa T, Motegi M, Hayami T, Asano S, Asano-Hayami E, Nakai-Shimoda H, Inoue R, Yamada Y, Miura-Yura E, Morishita Y, Himeno T, Tsunekawa S, Kato Y, Nakamura J, Kamiya H, Tominaga M. Thermal gradient ring reveals thermosensory changes in diabetic peripheral neuropathy in mice. Sci Rep. 2022 Jun 13;12(1):9724. doi: 10.1038/s41598-022-14186-x. PMID: 35697861; PMCID: PMC9192750.
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