Thermal hypersensitivity induced by chemogenetic stimulation of primary somatosensory neurons.

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Optogenetic tools such as the opsin ChR2 have been validated as pain-eliciting inducers when expressed in several subtypes of dorsal root ganglia (DRG) neurons expressing the voltage-gated sodium channel $Na_V1.8$. However, while excitatory ChR2 is known to evoke action potentials through direct ionotropic transduction, the chemogenetic actuator hM3Dq, an excitatory DREADD, works through metabotropic Gq-linked signaling. The behavioral outcome of neuronal activation via these heterologous actuators can therefore be quite different. We have reported that ionotropic activation using ChR2 versus metabotropic activation using hM3Dq evokes radically distinct responses when expressed in the MrgprA3+ subtype of DRG neurons.

Here we show that broad stimulation of adult TRPV1-expressing neurons, using virally-expressed hM3Dq, does not elicit directly observable pain responses but instead sensitizes these afferents. Specifically, hM3Dq-driven activation enhances their sensitivity to thermal stimuli. Electrophysiological evidence suggest that this is partially achieved through potentiation of the transient receptor vanilloid 1 (TRPV1) channels and our calcium imaging data validate this mechanism Interestingly, inflammation is not observed while stimulating the TRPV1+ neurons with the DREADD-selective agonist CNO.

Our aim is to further explore why and how DREADD activation in primary somatosensory afferents can elicit such selective cellular and behavioral responses.

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