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The Differing Effects Of Various TRPV1 And TRPA1 Antagonists On Capsaicin- And Mustard Oil- Induced Changes In Blood Flow In Mice.

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The Transient Receptor Potential Vanilloid 1 (TRPV1) and Ankyrin 1 (TRPA1) ion channels are part of the TRP superfamily of receptors and are both integrators of noxious stimuli. Both channels are typically expressed on primary sensory neurons although both receptor types are expressed and functional on other cell types (Fernandes et al., 2012). TRPV1 is activated by various agonists, including capsaicin, heat >43°C. Capsaicin has differing effects on the vasculature of the ear and knee synovial membrane, due to neuronal (ear) versus non-neuronal (synovial membrane) TRPV1 activation (Keeble & Brain, 2006; Kark et al., 2008). TRPA1 is also activated by many agonists, including mustard oil and cinnamaldehyde. The vascular responses to mustard oil in the ear and knee synovial membrane are less well characterised than the capsaicin responses and relative involvement of neuronally and non-neuronally expressed TRPA1 has not been elucidated.

This study determined the capacity of the TRPV1 antagonists SB366791 (Gunthorpe et al., 2004) and JNJ17203212 (Swanson et al., 2005), and the TRPA1 antagonists TCS5861528 (Wei et al., 2011) and HC030031 (Eid et al., 2008) to inhibit capsaicin- and mustard oil-induced (respectively) changes in blood flow in the murine pinna and knee synovial membrane.

Male and female CD1 mice (25-35g, Charles River, UK) were used for all experiments in accordance with the Scientific Procedures Act (1986). Orally administered compounds were given in a volume of 5ml/kg, peritioneally administered compounds in 10ml/kg. All drug doses used possess proven analgesic efficacy. JNJ17203212 (n=6; 30mg/kg i.p. in 10% DMSO; Tocris, UK), and SB366791 (n=7; 5mg/kg i.p. in 2% DMSO; Sigma, UK) were administered one-two hours before capsaicin or vehicle (100% ethanol) was applied to the pinnae and exposed knee joint synovial membranes of ketamine -anaesthetised mice and blood flow was measured by laser Doppler imagery (Moor instruments). TCS5861528 (n=6 10mg/kg p.o in 2% DMSO; Tocris, UK) and HC030031 (n=6 100mg/kg p.o in 10% DMSO; Sigma UK) were administered one hour before mustard oil or vehicle (paraffin oil in pinna, 100% ethanol in the exposed knee joint synovial membrane) were applied to the same sites.

Whilst mustard oil caused an increase in blood flow in the pinna and knee synovial membrane, capsaicin caused an increase in blood flow in the pinna but a decrease in blood flow in the knee synovial membrane. This decrease is most likely due to non-neuronal TRPV1 activation. SB366791 had no significant effect on capsaicin-induced vascular responses whilst JNJ17203212 significantly attenuated the capsaicin response in the pinna and the exposed knee synovial membrane ($P<0.05$, ANOVA). TCS5861528 had no significant effect on mustard oil-induced vascular responses whilst HC030031 reduced the mustard oil response at both sites. Interestingly, 5mg/kg SB366791 does not cause hyperthermia in mice (Fernandes et al., 2011) whilst 30mg/kg JNJ17203212 does (Fernandes et al., unpublished data).

References:

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