

The capsaicin receptor, TRPV1, as a target for chronic pain therapy

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Chronic pain is a debilitating and distressing condition which affects more than 300 million people worldwide. It is more prevalent in older populations and its incidence is increasing due to greater longevity. Current therapies are less than adequate and new therapies are needed. This presentation will review the basis of sensation of chronic pain and the potential of the transient receptor potential V1 (TRPV1) channel as a novel target for chronic pain therapy. I recently led a drug discovery program at Novartis Pharma R&D which developed antagonists of the heat-sensitive TRPV1. This group was the first to show the effectiveness of a TRPV1 antagonist (capsazepine) in reversing pain behaviors in animal models of chronic neuropathic and inflammatory pain (Walker *et al.*, 2003) and developed an orally active antagonist which was also successful in reversing pain behaviour in inflammatory and neuropathic models (Culshaw *et al.*, 2006). This and subsequent medicinal chemistry programs from other companies have generated TRPV1 antagonists which are effective in reversing pain behaviors in animal models of chronic pain and novel compounds from several pharmaceutical companies have entered clinical trials. Preliminary phase 1 studies are reporting interesting results. Thus, a phase 1b trial of the TRPV1 antagonist AMG-517 could not be completed because of a significant hyperthermia in all patients (Gavva *et al.*, 2008). Another TRPV1 antagonist, SB-705498 successfully reversed the hyperalgesia of a UV-induced burn and was not observed to cause hyperthermia (Chizh *et al.*, 2007). The different observations made regarding hyperthermia in these two trials could be due to off-target effects, differential exposure of the brain to the antagonists or different mechanisms of action via activity at qualitatively different forms of TRPV1. We have been investigating possible post-translational modifications of this ion channel which may have relevance to this observation. To this end, we have generated and partially characterized a series of Chinese hamster cell lines expressing a comprehensive array of rat TRPV1 variants with mutations of the major phosphorylation sites that have previously been reported for this receptor.

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