DEVELOPMENT OF VERY POTENT AND SELECTIVE LIGANDS AT TRPV1 CHANNELS AND THEIR THERAPEUTIC POTENTIAL

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Recent acquisitions on the molecular biology, distribution and role of the transient receptor potential vanilloid 1 (TRPV1) have greatly strengthened previous hypothesis that this channel may exert important functions in different pathophysiological conditions, and specifically in pain and inflammatory diseases. Treatment with capsaicin resulting in desensitization of nociceptive sensory neurons have been proven to ameliorate various pain conditions, thus suggesting that TRPV1 could be a potential target for the development of novel analgesics. TRPV1 agonists share with capsaicin the ability to desensitize the nerve terminals that express the stimulated channels. In this manner the sensory neuron becomes non-responsive to potential pain producing stimuli. and TRPV1-mediated desensitization provides an analgesic effect. This approach is being continuously studied with capsaicin and capsaicin analogues in various clinical conditions. An alternative way to target theTRPV1 is though the development of selective channel antagonists. TRPV1 knockout mice showed a marked impairment of thermal hyperalgesia, whereas mechanical hyperalgesia appeared to be unaffected. Similarly, early developed TRPV1 antagonists, including capsazepine, were reported to be ineffective in reducing mechanical hyperalgesia. Programs of development of specific and high affinity TRPV1 antagonists have produced a large variety of compounds and some of these have been tested in models of neuropathic pain or inflammatory pain. There is now evidence that certain TRPV1 antagonists show efficacy in reducing mechanical hyperalgesia in experimental animals and are currently undergoing clinical testing. In addition to pain research there are further areas where TRPV1 antagonists may find a future clinical application. Among these, there are conditions characterized by overactivity of reflex responses, where the initiation of the pathological response can be recognized in the stimulation of TRPV1-expressing sensory neurons. Because symptoms of the overactive bladder syndrome are hypothesized to be mediated by TRPV1 activation, TRPV1 antagonists are considered to exert a beneficial effect in these condition. Capsaicin is a well known stimulus to induce cough in experimental animals and in man, and patients with various airway diseases show a lowered threshold to capsaicin-induced cough. Thus, an additional clinical application of TRPV1 antagonists is the treatment of chronic cough. Finally, TRPV1 has been reported to be activated by a large variety of chemical and physical stimuli, and interestingly, it undergoes marked upregulation by a number of intracellular and extracellular mediators involved in the mechanisms of various inflammatory and pain diseases. TRPV1 antagonists may indirectly reduce the proinflammatory and proalgescic actions of those stimuli that, at least in part, act through TRPV1 activation.