TRPV1 Modulation of Plasticity in the Hippocampus

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INTRODUCTION

Learning and memory are phenomena made possible via physical changes at neuronal synapses in the brain, a process known as synaptic plasticity. Dysfunction in synaptic plasticity can contribute to such diseases and disorders as Alzheimer’s Disease, Parkinson’s Disease, and retrogade amnesia (Brun et al., 2001). Recently, TRPV1’s activation was shown to mediate calcium sensitivity in the hippocampus (Gibson et al., 2002). TRPV1 is a non-selectivecation (Ca2+) channel located throughout the CNS, including the hippocampus. TRPV1’s channels are activated by the binding of capsaicin, which is responsible for producing the “hot” of red peppers. Several studies implicate a role for TRPV1 in contextual fear learning (March et al., 2007), recall of spatial memory (Li et al., 2008), and anxiety-related disorders (Santos et al., 2007), indicating depression (Kawasaki et al., 2004). Using field electrophysiological recording in CA1 stratum radiatum we measured high frequency stimulation or theta burst-induced LTP in the presence of capsaicin (10 µM) antagonist. TRPV1 antagonist and picrotoxin (1 µM). Our data suggest that TRPV1’s role in mediating increased LTP is not expressed at the CA1-Caj nucleus, but possibly at the CA1-interneuron synapse. Further, we propose a novel mechanism by which TRPV1 activation enhances hippocampal CA1 pyramidal cell LTP via modulation of inhibitory interneurons circuit.

QUESTION / OBJECTIVE

TRPV1 receptors have recently been demonstrated to mediate long-term depression of hippocampal CA1 stratum radiatum slices (March et al., 2007). This shows that TRPV1 is sensitive to capsaicin (10 µM) and 100 µM capsaicin induced LTP is not directly enhanced by picrotoxin (1 µM). TRPV1 knock-out mice are resistant to radiation-induced LTP and show reduced long-term depression activity in wild-type mice (March et al., 2007) and application of high doses of the TRPV1 agonist capsaicin induced CA1-LTP in wild type rats (Li et al., 2008). However, the mechanism mediating TRPV1’s influence on CA1-LTP is not known. We investigated whether LTP modulation by TRPV1 might play a role in mediating increases in CA1-LTP.

METHODS

Preparation of Brain Slices

Brain slices were obtained from 16-37 day-old mixed sex and female Sprague-Dawley rats. All experiments were performed in accordance with Institutional Animal Care and Use Committee (IACUC) guidelines. Slices were cut into 200 µm thick coronal slices, obtained using a sterile brain veran, were stored at room temperature for at least 1 hour to ensure a resting membrane potential of 20 mV. During recording, a tungsten electrode filled with 2 M NaCl was placed in the CA1 stratum radiatum and synaptic currents were induced using a bipolar stimulating electrode located 400-600 µm away from the recording electrode (Figure 1A). Stimuli (intensity typically 0.5-5.0 µA, 15 ms duration) were delivered at 0.1 Hz and the current intensity was adjusted until a resting membrane potential of approximately 0.85 mV at the start of each experiment. Following conditioning with either theta-burst (two bursts of 5 pulses at 100 Hz, repeated at 200 ms intervals ten times) or high frequency stimulation (electrical stimulus of approximately 1 mV at 10 Hz) bilateral, pyramidal cell exhibited LTP. For the majority of the experiments reported here, theta-burst stimulation was used, as this protocol more closely simulates the natural firing patterns in the brain. In the presence of Capsazepine (specific TRPV1 agonist) and antagonist, respectively) in conjunction with picrotoxin (1 µM TRPV1 antagonist), the LTP response of pyramidal cells with and without TRPV1 agonist activity were compared, including a series of picrotoxin experiments allowing comparison of experiments with and without the inhibitory effect of GluK2-containing interneurons.

CONCLUSIONS

Capsazepine (10 µM) was sensitive to 100-1000 µM capsaicin, but not present at the CA1-Caj pyramidal cell synapse (Figure 2B), unlike the CA1-interneuron synapse (Figure 2A). We did observe that TRPV1 activation by capsaicin enhances hippocampal CA1 pyramidal cell LTP, and that picrotoxin-mediated blockade of GluK2-containing inhibitory interneurons decreases capsaicin-induced LTP. This suggests that TRPV1 receptors involved in enhancing CA1 LTP are present on pyramidal cells or interneurons or regulate interneuron activity, rather than acting directly on CA1 pyramidal cells.

SIGNIFICANCE

TRPV1 was first classified and described as a heat-activated ion channel expressed in peripheral sensory neurons (Caterina et al., 1997), and much of this research has centered on the possible role of TRPV1 agonists and antagonists in various inflammatory or neuropathic pain (Gibson et al., 2008). Based on this and other studies (March et al., 2007; Li et al., 2008; Gibson et al., 2008), it is clear that TRPV1 also plays an important role in the CNS. Behavioral studies have described the effects of TRPV1 activation and blockade on anxiety-related behaviors, depression, learning, and spatial memory recall (Santos et al., 2008; Kawasaki et al., 2004; March et al., 2007; Li et al., 2008). Indeed, the results of the current study implicate that synaptic plasticity, the most likely mechanism of learning and memory, is directly regulated by TRPV1 activation (Figure 4B). In addition, it has been hypothesized that TRPV1’s channels may become active in response to the high temperatures of fever, which may lead to the hypersensitivity of pyramidal cells that results in fever symptoms (Gibson et al., 2008). Taken together, these findings indicate that drugs that bind to CNS-TRPV1 receptors have many beneficial effects not previously considered. The present research demonstrates, and produces drugs that target TRPV1’s for its ability to mediate pain in the peripheral nervous system should take into careful consideration the effects of such drugs on the brain.

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