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Microreview of Transient Receptor Potential Vanilloid 4

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Transient Receptor Potential Vanilloid 4 plays keys roles throughout the body. This is due to its massive expression across cells of different systems. It is involved in inflammation response, the development of osteoarthritis, and energy homeostasis. Through knockout genes for TRPV4 it has been shown that insulin resistance can improve as well as resistance to obesity. Through activation of the channel it has been shown to initiate the influx of calcium predominantly in its signal transduction, but also facilitates intracellular calcium release in chondrocytes. Through antagonists research indicates that TRPV4 may be useful in treating diabetes and obesity as well. By possible reduction of a chronic inflammatory state TPRV4 could have many targeted medical applications in future years.

Introduction

Transient Receptor Potential Vanilloid 4 will be the main topic of interest. This is a cation channel of the Transient Receptor Potential family, and is a membrane bound environmental sensor used by the cell to receive stimuli.TRPV4 is able to respond to multiple types of stimuli including thermal, osmotic, chemical, and mechanical stimuli. This channel is widely expressed throughout the body and regulates many functions and transcription of genes. It is still widely unknown how exactly it functions throughout the body. Recent research has indicated this channel as an appropriate target to help combat many chronic diseases in humans but no practical application has been found. With its involvement in cartilage maintenance, inflammation response, and energy expenditure it is obvious that we can learn much about these systems through further investigation of TPVR4. TPVR 4 is also affected by other receptors in the cell and responses could possibly be mediated through these avenues.

Recent Progress

Chondrocytes are the cells that maintain the extra cellular matrix (ECM) of cartilage throughout the body. These cells must be responsive to their extracellular environment but the way this is accomplished through signal transduction is not fully comprehended. Transient receptor potential vanilloid 4 (TRPV4), an osmotically gated ion channel, specifically in the form of the calcium ion, is thought to play a role in this and was the area of interest in the research performed by M. N. Phan et all. Osteoarthritis (OA) is characterized by the decline of the cartilage ECM. Discovering how these cells sense their environment and how this impacts ECM production and maintenance is important if we are to find ways to combat this prevalent disease. In OA swelling results from damage to the collagen network which lowers the interstitial osmotic pressure. Interlukein-1 has been shown to prevent volume regulation of the chondrocytes by affecting Calcium ion (Ca+) transients of the cell as well as being an activator of the pro-inflammatory cytokine COX-2. This study aimed to address if TRPV4 played a role in the chondrocytes response to IL-1 and if it played a role in volume regulation of the cell as well as conduct Ca+ in response to osmotic stress. Pig chondrocytes were cultured for this experiment and used as the model system. Through immunohistochemistry with TRPV4 antibodies the channel was clearly expressed in the pig chondrocytes. From application of a TRPV4 agonist 4aPDD, induction of the influx of CA+ ion occurred. A TRPV4 antagonist GSK205 was also shown to block the

CA+ influx. Iso-osmotic medium was not shown to have a significant effect on Ca+ influx. Osmotic stress, both hypo- and hyper-, did induce Ca+ influx on chondrocytes however. This response was shown to decline when exposed to the antagonist GSK205 as well. Maximum volume was increased in hypo-osmotic conditions but this was decreased with the addition of GSK205. A decrease in regulatory volume was also inhibited by blocking TRPV4 activation with GSK205. IL-1 treated cells showed reduced regulatory volume decrease that was then eliminated by activation of TRPV4 through 4aPDD. This experiment established that TRPV4 is in fact responsible for calcium induction by demonstrating that an agonist 4aPDD induced Ca+ influx that could then be blocked by the application of an antagonist GSK205. It was also shown that blocking of TRPV4 inhibited the volume and Ca+ responses in hypo-osmotic stress. This suggests that TRPV4 plays a critical role in osmotically regulated signal transduction in chondrocytes. This gives evidence to support the fact that TRPV4 may act as mechanoreceptor, and regulate cellular response in cartilage since loading of joints directly impacts interstitial osmolarity. Further insight may enlighten us further on regulation of cartilage development and therefore its prevention of decay.

In the work conducted by A. Denadai-Souza ET all, they set out to discover if TRPV4 induces inflammation in a rat temporomandibular joint (TMJ). TRPV4 is a membrane environmental that can sense changes in thermal, osmotic, chemical, and mechanical stimuli. It is widely expressed in vascular, musculoskeletal, and sensory systems. TRPV4 can be sensitized by exposure to proinflammatory chemicals like prostaglandin, histamine or serotonin which causes increased pain reception to hypo-, or hyper-tonic, and mechanical stimulants. Activation of protease-activated receptor 2 (PAR2) has been shown to induce inflammation within the TMJ, this receptor is also dependent upon calcium intake by TRPV4 leading to an interaction between the receptors. The function of TRPV4 was assessed by measuring the influx of calcium of cells of the TMJ as well as trigeminal ganglion neurons (TG). Inflammation was induced by injection of carrageenan, a proinflammatory molecule, into the TMJ. These neurons were later removed and mounted for analysis. TRPV4 was found to be widely expressed in the rat TMJ, especially in the cartilage. Intense expression was also found in the TG neurons. It was also found that the TRPV4 agonist 4aPDD induced a concentration dependent increase in Ca+ influx. PAR2 expression was also observed in the TMJ and TG neurons indicating a co expression of receptors. Using real time reverse transcriptase PCR it was also found that both mRNA for PAR2 and TRPV4 had been up regulated only 4 hours after injection of carrageenan, in the TMJ, but only TRPV4 was up regulated in TG neurons. Activation of PAR2 through the PAR2 activating peptide (PAR2-AP) caused an increase in the calcium response action of TRPV4. It was also shown that treatment of agonists PAR2-AP and 4aPDD caused dose dependent increase in plasma extravasation (inflammation) in the TMJ and TG neurons. These findings indicate that the sensory capabilities of TRPV4 serve a protective role in the homeostasis of the musculoskeletal system especially the joints. This study also shows that TRPV4 is expressed in cells that are clearly involved in the pathophysiology of arthritis, and upon activation produces pain and inflammation. The results also lead us to believe the coexpression of TRPV4 and PAR2 will serve to potentiate the inflammatory response in rats. Further studies are required to demonstrate these interactions in humans however.

Brown adipose tissue is able to uncouple respiration from ATP synthesis and dissipate energy effectively as heat. This is accomplished by Uncoupling Protein 1 (UCP1). Transcriptional regulators of UCP1 include PGC1a which will be the topic of the experiment composed by L. Ye, ET all. PGC1a is involved in many transcription factors and plays a role in mitochondria synthesis and oxidative metabolism. PGC1a expression is induce by cold and b-andrenergic systems in adipose tissue, trying to find a chemical compound to increase PGC1a expression would prove useful in combating many diseases. After using quantitative PCR to identify molecules to induce PGC1a, an antagonist of TRPV4, was found to achieve such results. Adipose tissue was then shown to have high levels of TRPV4 expression, especially in white adipose tissue compared to brown. It was then found that using knockout RNA (shRNA against TRPV4) to stop expression of TRPV4 resulted in a 3 times increase of induction of PGC1a compared to normal TRPV4 cells. This indicates that TRPV4 is a negative regulator of oxidative metabolism and respiration in adipocytes. The increase of PGC1a, and consequently UCP1 and other genes, propose a browning of the white adipose tissue, that is they have more characteristics of the brown adipocytes. The knockout adipocytes showed increases in maximal respiration compared to non-knockout. They also showed as in previous studies that activation of TRPV4 resulted in a proinflammatory state. The knockout adipocytes also showed lower expression of inflammatory cytokines. They then conducted comparisons with mice containing a knockout gene for TRPV4 and control mice. In knockout mice, after being fed a high fat diet, less weight gain was observed after 9 weeks when compared to control group. Energy expenditure was also increased in knockout mice, showing that it may be due to increased thermogenesis

from gene alteration. Knockout mice also showed improved insulin sensitivity by observing reduced fasting and glucose-stimulated insulin levels. This makes TRPV4 a target for obesity and insulin resistance. Treatment of antagonists for TRPV4, was also accompanied by a decrease in proinflammatory genes, and an increase in thermogenic genes UCP1, and PCG1a, and improved glucose tolerance which largely resembled the knockout mice.

Discussion

TRPV4 may have many medical uses as a target to help combat chronic diseases plaguing us today. The regulatory effect TRPV4 has on obesity in particular is extremely curious. If we could somehow manipulate this channel to reduce its proinflammatory actions while also inducing thermogenic, and mitochondrial gene production we could actually find a significant weapon in the war on diabetes, and weight gain. We must first learn what negative effects may arise in antagonizing this channel throughout the body. It has already been shown that alterations to the TRPV4 gene can lead to many musculoskeletal disorders in humans, as it serves to respond to the ECM of chondrocytes. Perhaps with targeted antagonization of only certain cell types, namely adipocytes, we may be able to deter these negative outcomes while still enjoying the positive changes it can bring. Still further research is needed to fully understand how this channel operates. One area that is also of interest is the other Transient Receptor Potential Vanilloids, namely 1 and 8 which could serve as another path to achieve the desired treatments that seem possible with TRVP4.The work shown with rats is promising but it will be a long time still before we have human application.

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