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Warming Up to New Possibilities with the Capsaicin Receptor TRPV1: mTOR, AMPK, and Erythropoietin

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Abstract

BACKGROUND—Transient receptor potential (TRP) channels are a superfamily of ion channels termed after the *trp* gene in *Drosophila* that are diverse in structure and control a wide range of biological functions including cell development and growth, thermal regulation, and vascular physiology. Of significant interest is the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor, also known as the capsaicin receptor and the vanilloid receptor 1, that is a non-selective cation channel sensitive to a host of external stimuli including capsaicin and camphor, venoms, acid/basic pH changes, and temperature.

METHODS—Given the multiple modalities that TRPV1 receptors impact in the body, we examined and discussed the role of these receptors in vasomotor control, metabolic disorders, cellular injury, oxidative stress, apoptosis, autophagy, and neurodegenerative disorders and their overlap with other signal transduction pathways that impact trophic factors.

RESULTS—Surprisingly, TRPV1 receptors do not rely entirely upon calcium signaling to affect cellular biology, but also have a close relationship with the mechanistic target of rapamycin (mTOR), AMP activated protein kinase (AMPK), and protein kinase B (Akt) that have roles in pain sensitivity, stem cell development, cellular survival, and cellular metabolism. These pathways with TRPV1 converge in the signaling of growth factors with recent work highlighting a relationship with erythropoietin (EPO). Angiogenesis and endothelial tube formation controlled by EPO requires, in part, the activation of TRPV1 receptors in conjunction with Akt and AMPK pathways.

CONCLUSIONS—TRPV1 receptors could prove to become vital to target disorders of vascular origin and neurodegeneration. Broader and currently unrealized implementations for both EPO and TRPV1 receptors can be envisioned for for the development of novel therapeutic strategies in multiple systems of the body.

Keywords

Akt; aging; aging-related disorders; Alzheimer's disease; AMP activated protein kinase (AMPK); angiogenesis; apoptosis; autophagy; cardiovascular disease; diabetes mellitus; endothelial cells; epidermal growth factor; erythropoietin; hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2); endothelial cells; hyperthermia; mechanistic target of rapamycin (mTOR); mTOR Complex 1 (mTORC1); mTOR Complex 2 (mTORC2); metabolism; nerve growth factor;

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nicotinamide; nicotinamide adenine dinucleotide (NAD^+); proline rich Akt substrate 40 kDa (PRAS40); oxidative stress; pain; phosphoinositide 3-kinase (PI 3-K); programmed cell death; silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1); sirtuin; stem cells; thermoregulation; transient receptor potential; TRPV1; vanilloid receptor 1

The TRP Superfamily and TRPV1

Transient receptor potential (TRP) channels are a superfamily of ion channels that consists of 28 cation channels (1). This superfamily of TRP channels is termed after the *trp* gene in *Drosophila* that upon mutation leads to a transient receptor potential following light exposure. TRP channels are diverse in structure and as a result can modulate transduction of thermal, chemical, and mechanical stimuli and also can control cell differentiation, cell growth, and vascular physiology (2–4).

Of particular interest is the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor, also known as the capsaicin receptor and the vanilloid receptor 1. The TRPV1 receptor is a non-selective cation channel with a preference for calcium transmission and was initially identified as a specific receptor for capsaicin that causes a burning sensation. TRPV1 is a polymodal receptor and is sensitive to multiple external stimuli that include capsaicin and camphor, venoms from arachnids and jellyfish, ethanol, linoleic acid metabolites, temperature above 43°C (109.4 °F), and acid/basic pH changes.

TRPV1 receptors also may impact multiple biological pathways and cellular survival. Sensitization of TRPV1 can be controlled through phosphorylation by protein kinase A, protein kinase C, phospholipase C, and phosphatidylinositol-4,5-bisphosphate (PIP_2). In relation to cellular survival, TRPV1 may either benefit or limit cell injury potentially based on the underlying mechanisms activated. For example, during periods of cerebral ischemia, TRPV1 may increase cytosolic calcium accumulation in neurons and lead to apoptotic cell death (5). TRPV1 receptors also have been implicated in apoptotic cell death in retinal ganglion cells during pressure –related insults (6). Apoptosis is not the only form of programmed cell death that involves TRPV1. These receptors also can influence pathways tied to autophagy (7, 8). During oxidative stress (9), some studies suggest that TRPV1 receptor activation may promote autophagy that can be protective and enhance cellular survival (10)

TRPV1 in Neuronal and Vascular System Injury

TRPV1 receptors play a role in the nervous and vascular systems and my have clinical relevance to degenerative disorders (11, 12). In studies that examine high-fat diets and obesity in animal models, TRPV1 can control vasodilatory and vasoconstrictor responses that may increase the risk for developing headache disorders (13). Yet, additional studies suggest other functions for TRPV1 in metabolic disorders and diabetes (14, 15). TRPV1 activation has been reported to prevent endothelial dysfunction during periods of hyperglycemia (16). In studies that involve dementia (12, 17), TRPV1 activation can lessen cellular injury, oxidative stress, and vascular dementia (18). TRPV1 activation also may reduce Alzheimer’s disease like pathological stress during animal models that employ cold

water stress (19) and may limit hyperphosphorylation of tau protein in models of Alzheimer's disease (20). Loss of TRPV1 has recently been associated with the exacerbation of hyperthermic seizures (21), a disorder that may be linked to multiple pathways (22)

TRPV1, mTOR, AMPK, and Akt

A number of signal transduction systems may work in conjunction with TRPV1 receptors that ultimately determine the role of these receptors in different systems of the body. Interestingly, the mechanistic target of rapamycin (mTOR) has been demonstrated to control pain hypersensitivity following tissue injury. mTOR is considered a vital component that affects multiple cellular pathways (11, 23–29). mTOR also is known as the mammalian target of rapamycin and the FK506-binding protein 12-rapamycin complex-associated protein 1 (30). The target of rapamycin (TOR) was first documented in *Saccharomyces cerevisiae* with the genes *TOR1* and *TOR2* (31). Through the use of rapamycin-resistant TOR mutants, *TOR1* and *TOR2* were found to encode the Tor1 and Tor2 isoforms in yeast. TOR and mTOR activity can be blocked by rapamycin, a macrolide antibiotic in that exists in *Streptomyces hygroscopicus*.

mTOR is encoded by a single gene *FRAP1* and is the principal component of the protein complexes mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (32). mTORC1 contains the components Raptor, Deptor (DEP domain-containing mTOR interacting protein), the proline rich Akt substrate 40 kDa (PRAS40), and mammalian lethal with Sec13 protein 8, termed mLST8 (mLST8/GβL) (33). mTORC2 consists of Rictor, Deptor, mLST8, the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) (34).

Critical to mTOR signaling are AMP activated protein kinase (AMPK) (15, 35, 36) and protein kinase B (Akt) (11, 23, 37). AMPK can govern cellular metabolism, cell survival, and inflammation (25, 38–41). AMPK inhibits mTORC1 activity through the activation of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex. TSC2 is a GTPase-activating protein (GAP) converting G protein Rheb (Rheb-GTP) into the inactive GDP-bound form (Rheb-GDP). Once Rheb-GTP is active, Rheb-GTP combines with Raptor to oversee the binding of the eukaryotic initiation factor 4E (eIF4E)-binding protein 1 (4EBP1) to mTORC1 that will lead to an increase in mTORC1 activity (42). AMPK can phosphorylate TSC2 to increase GAP activity to change Rheb-GTP into the inactive Rheb-GDP and to inhibit mTORC1 activity (43). AMPK also can increase nicotinamide phosphoribosyltransferase (NAMPT) activity to convert nicotinamide to nicotinamide mononucleotide (31, 44, 45). This conversion of nicotinamide increases nicotinamide adenine dinucleotide (NAD^+) levels and decreases levels of the silent mating type information regulation 2 homolog 1 *(Saccharomyces cerevisiae*) (SIRT1) inhibitor nicotinamide (39, 46, 47).

Both Akt and phosphoinositide 3-kinase (PI 3-K) also have a vital role in the mTOR signaling pathway (15, 37, 48–50). mTOR contains terminal domains that oversee the binding, catalytic activity, and phosphorylation of mTOR (51). In regards to the C-terminal domain of mTOR, this domain has a sequence homology to the catalytic domain of the PI 3-

K family and contains several phosphorylation sites that regulate mTOR. Downstream from PI 3-K, Akt can prevent TSC1/TSC2 complex activity that would then allow the activation of mTORC1 (52, 53). Control of the TSC1/TSC2 complex is principally mediated though the phosphorylation of TSC2 by Akt. Akt can phosphorylate TSC2 on several sites that leads to TSC2 destabilization and disruption of TSC2 association with TSC1. Phosphorylation of TSC2 at serine^{939}, serine^{981}, and threonine^{1462} results in the binding of TSC2 to cytoplasmic protein 14-3-3, disengagement of the TSC1/TSC2 complex, and activation of Rheb and mTORC1 (54).

mTOR has been shown to be necessary for thermal hypersensitivity following dorsal root ganglion incision mediated through vesicular glutamate transporter 2 expression and TRPV1 receptors (55). Yet, mTOR pathways may lead to other scenarios with TRPV1 receptors depending upon the circumstances. During studies with pressure overload-induced cardiac hypertrophy and contractile dysfunction, increased expression of TRPV1 receptors with AMPK phosphorylation and autophagy activation appears to mediate injury mechanisms during cold stress (56). TRPV1 also relies upon the AMPK pathway to activate autophagy and block foam cell formation in vascular smooth muscle cells (57). Similar pathways for the induction of autophagy by TRPV1 and AMPK have been shown in thymocytes (58). In regards to Akt, TRPV1 is dependent upon the activation of Akt in the dorsal root ganglion for pain sensation (59). In relation to blocking the progression of Alzheimer's pathology, activation of Akt during TRPV1 receptor activity appears necessary to prevent hyperphosphorylation of tau protein (20). Furthermore, in pathways involving the epidermal growth factor (EGF) receptor and Akt, TRPV1 activation can control human corneal epithelial cell proliferation and migration (60).

TRPV1 and Erythropoietin

In addition to the varied pathways associated with TRPV1 signaling, TRPV1 receptors are also linked to trophic factors. As previously described, TRPV1 activation can control human corneal epithelial cell proliferation and migration through the EGF receptor (60). Other work suggests that nerve growth factor (NGF) is closely associated with TRPV1 signaling. NGF can lead to neuritogenesis through mechanisms that rely upon the translocation of TRPV1 to the cell surface (61). NGF also can control nociception through enhanced TRPV1 activity (62).

Recently, another trophic factor, namely erythropoietin (EPO), has been shown to oversee TRPV1 signaling. The *EPO* gene is located on chromosome 7 and is a single copy in a 5.4 kb region of the genomic DNA (63). This gene encodes for a polypeptide chain protein that has initially 193 amino acids (64). EPO is then processed with the removal of a carboxy-terminal arginine^{166} in the mature human and recombinant human EPO (rhEPO). A protein of 165 amino acids with a molecular weight of 30.4 kDa is subsequently generated (65–68). EPO, an erythropoiesis-stimulating agents, is approved for the treatment of anemia that results from chronic kidney failure, human immunodeficiency virus, and chemotherapy. EPO is present in the brain, uterus, and liver (69–73), but the primary site for the production and secretion of EPO is the kidney peritubular interstitial cells. EPO expression is overseen by changes in oxygen tension and not by the concentration of red blood cells (69, 74, 75).

EPO and TRPV1 share a number of overlapping pathways that include mTOR, AMPK, and Akt. For example, EPO governs pathways of apoptosis and autophagy through mTOR. EPO can block apoptotic cell death during amyloid exposure through mTOR to prevent caspase activation (76) and EPO can promote microglial survival during oxidative stress through mTOR signaling (77). In addition, EPO governs mTOR and down-stream signaling pathways that involve proline rich Akt substrate 40 kDa (PRAS40) to enhance neuronal survival during oxygen-glucose deprivation (78). EPO also relies upon mTOR during hypoxia-reoxygenation stress to protect hippocampus-derived neuronal cells (79).

EPO also blocks autophagy through mTOR activation (31, 80, 81). mTOR is a principal pathway to control autophagy since activation of mTOR blocks autophagy by phosphorylating autophagic related genes (*Atg*) and proteins that include Atg13 and UNC-51 like kinases (ULKs) to inhibit the UNC like kinase complex ULK-Atg13-FIP200 (52). EPO can promote cellular protection during hypoxia and oxidative stress in retinal progenitor cells by preventing the induction of autophagy (82). EPO also can prevent excessive autophagy that precedes apoptosis during experimental neonatal necrotizing enterocolitis (83). By reducing the activity of autophagy, EPO limits neonatal brain damage in the developing rodent during hyperoxia exposure and oxygen toxicity (84).

In the mTOR signaling pathway, EPO also relies upon AMPK. It should be noted that some activity of autophagic pathways may be required for EPO protection. In some cases, EPO can protect against neurotoxicity through increased AMPK activity and enhanced autophagy activity (85). EPO also can control AMPK and mTOR activities to protect cells under conditions of oxidative stress (53). EPO also relies upon AMPK pathways for anti-oxidant gene expression (45). EPO controls inflammation in the nervous system through AMPK (86) and EPO blocks apoptotic cell injury through AMPK and increasing autophagy-related signaling pathways (85).

Similar to mTOR and AMPK, PI 3-K and Akt are vital pathways that offer cellular protection through EPO. EPO can phosphorylate Akt at serine^{473} to activate Akt (37, 64, 87, 88). EPO signaling through Akt activation has been shown to protect against hypoxia-reoxygenation stress (79) and EPO may control intracellular calcium levels to preserve mitochondrial function (31, 67, 89–91). EPO also can increase cell survival through Akt activation during amyloid toxicity (92–94), oxidative stress (77, 78, 95–97), inflammation (98–100), and sepsis (101–103).

The recent observation that EPO can govern TRPV1 signaling is of significant interest and follows a logical course with the shared pathways known to exist for EPO and TRPV1 signaling. EPO has previously been shown to preserve endothelial function (95, 100, 104–106). Recent work now suggests that EPO maintains endothelial cell function, at least in part, through TRPV1 signaling. In endothelial cells, EPO led to the phosphorylation of Akt, AMPK, and endothelial nitric oxide synthase (eNOS) and the formation of a TRPV1-Akt-AMPK-eNOS complex that promoted endothelial tube formation. EPO also led to calcium cell influx during angiogenesis that was mediated through phospholipase C-γ1 (PLC-γ1) and resulted in TRPV1 activation. In the absence of TRPV1 signaling but with EPO present,

angiogenesis was blocked, suggesting that the TRPV1-Akt-AMPK-eNOS complex was a necessary component for endothelial tube formation and angiogenesis (107).

Future Perspectives

TRP channels are a fascinating superfamily of ion channels that oversee multiple biological functions such as cell development and growth, thermal regulation, and vascular physiology. As a member of this superfamily, TRPV1 is a non-selective cation channel and is sensitive to a host of external stimuli that include capsaicin and camphor, arachnids and jellyfish venoms, ethanol, linoleic acid metabolites, temperature above 43°C (109.4 °F), and acid/basic pH changes. TRPV1 receptors also affect multiple biological pathways that involve vasomotor control, metabolic disorders, cellular injury, oxidative stress, programmed cell death pathways of apoptosis and autophagy, and cognitive and neurodegenerative disorders. Interestingly, TRPV1 receptors do not rely only upon calcium signaling to impact cellular biology, but also have an intricate relationship with mTOR, AMPK, and Akt that play roles in pain sensitivity, stem cell development, cellular survival, and cellular metabolism. Ultimately these pathways converge with TRPV1 in the activity of trophic factors. Recent work demonstrates that the growth factor and cytokine EPO that is currently approved for the treatment of anemia and may have future applications for multiple disease entities that include neurodegenerative disorders such as Parkinson's disease (108) and dementia (109) relies upon TRPV1 for angiogenesis. EPO employs TRPV1 to oversee endothelial tube formation, suggesting that as an underlying mechanism TRPV1 could prove to be critical for future applications that are targets against both acute and chronic neurodegenerative insults. Broader implementations for both EPO and TRPV1 receptors could easily be envisioned with additional research to develop therapeutic agents for a number of disorders throughout the body.

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