Pharmacology Of Vanilloid Receptors

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The spicy history of vanilloid receptors can be traced back to the discovery of red hot chilli peppers 6000 years back. Capsaicin - Important component that rendered the spicy nature to these and made them a culinary and medicinal wonder was discovered to be a lipophilic vanilloid compound. From the identification of capsaicin as a vanilloid compound and molecular cloning of vanilloid receptor by David Julius and validation of TRPV1 as a target for pain till recent FDA approval of topical capsaicin patch last month, vanilloid receptor poses as an enigma in the field of research. Role of vanilloid receptors have been explored in the field of pain and inflammation, migraine, degenerative disorders of CNS, IBD, thermoregulation and so on. This review will discuss vanilloid receptors under following aspects - History and introduction of vanilloid receptor, endogenous vanilloid, role of vanilloid receptor in health and disease, various agonists and antagonists finally the current status and prospects of vanilloid receptors in therapy.

Research Article

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ABSTRACT

The spicy history of vanilloid receptors can be traced back to the discovery of red hot chilli peppers 6000 years back. Capsaicin - Important component that rendered the spicy nature to these and made them a culinary and medicinal wonder was discovered to be a lipophilic vanilloid compound. From the identification of capsaicin as a vanilloid compound and molecular cloning of vanilloid receptor by David Julius and validation of TRPV1 as a target for pain till recent FDA approval of topical capsaicin patch last month, vanilloid receptor poses as an enigma in the field of research. Role of vanilloid receptors have been explored in the field of pain and inflammation, migraine, degenerative disorders of CNS, IBD, thermoregulation and so on. This review will discuss vanilloid receptors under following aspects - History and introduction of vanilloid receptor, endogenous vanilloid, role of vanilloid receptor in health and disease, various agonists and antagonists finally the current status and prospects of vanilloid receptors in therapy.

Keywords:
Receptor pharmacology, new drug target, vanilloid receptor, pharmacodynamics.

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INTRODUCTION:
Over the past few years, transient receptor potential (TRP) channels have become one of the most pursued targets not only in analgesic drug development but also in other disease states involving skin, bladder, CNS, airways and so on. TRP cation channel family comprises of 28 cation channels involved in various functions ranging from nociception, thermoregulation to bladder control. Out of the six subfamilies in TRP channels, transient receptor potential channels, of the vanilloid subtype (TRPV) has been known for its promiscuity in channel activation and interaction and thereby wide therapeutic implications. This review will summarize the important aspects in structure of TRPV and its subtypes and will provide a brief overview of TRPV in health and disease states and finally conclude by discussing the different agonists and antagonists at the receptor and future prospects.

TRP channel as therapeutic targets:[1,2]
TRP Channels are classified into 6 Subfamilies TRPC (Canonical), TRPV (Vanilloid), TRPCM (Melastatin), TRPA (Ankyrin), TRPP (Polycystin) and TRPML (Mucolipin)
General features of TRP channels:
- Low structural similarity, diverse function
- Six transmembrane domains (N and C domain)
- Homo-tetramers/hetero-tetramers
- Most members are cationic channels (calcium selective: TRPV 5 and 6, and sodium selective: TRPM 4 and 5)
- Noncanonical ions are also transported- iron (TRML), magnesium (TRPV6)
- Sensors of environmental temperature- even change in temperature of 10°C will bring change in activity.

TRPV1–Vanilloid receptor:
TRPV1, the most polymodal nonselective cation channel and the oldest yet most important member of vanilloid TRP family, was first cloned in rat dorsal root ganglion (DRG). TRPV1 has wide species diversity and diversity in its functions from integration of nociception and inflammatory hyperalgesia to its recent identification in the pathogenesis of Parkinson’s disorder.

History of vanilloid receptors: [3,4]
Capsaicin, the hot component of red chilly has opened up many new avenues in pharmacology of nociception and analgesia. First description of actions of capsaicin was made by Sir Nicholas Tesla and after few decades, the structure of capsaicin was linked to the receptor needed for its action and thus vanilloid receptor was cloned successfully in rat DRG by David Julius and his colleagues. With the structure activity relationship of capsaicin with vanilloid receptor in place, many capsaicin related molecules were synthesized and their role in activating VR was studied.

Biochemical pharmacology of vanilloid receptors:[5-16]
Molecular structure:
It consists of 6 membrane domains with a short pore forming region between the fifth and sixth domains. It comprises of long amino terminus with about 400-amino acid residues containing 3 ankyrin domains and a carboxy terminus containing TRP domain close to S6. It can form tetramers usually homo-tetramers and shows variable response to agonist and antagonists.

Properties of interest in vanilloid receptors:
1. Ligand gated non-selective cation channel
2. DRG and TG (Trigeminal ganglion) predominantely in C fibres but also in A fibres
3. Agonists: Capsaicinoids, resiniferanoids, unsaturated dialdehydes
4. Endogenous agonist: Proton
5. Synthetic agonist: Olvanil and nuvianil
6. Antagonist: Capsazepine, ruthenium red
7. Modulation of channel function: pH, metal cations, temperature

Table 1: Distribution of vanilloid receptors in humans:

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>TRPV1 (VR1), TRPV2 (VRL-1)</td>
<td>Sensory neurons TRPV2-macrophage</td>
</tr>
<tr>
<td>TRPV3 (VRL-3)</td>
<td>Keratinocytes</td>
</tr>
<tr>
<td>TRPV4 (VRL-2)</td>
<td>Trachea, kidney, spleen, testis, liver, heart</td>
</tr>
<tr>
<td>TRPV5 (ECAC1)</td>
<td>Kidney, small intestine, brain</td>
</tr>
<tr>
<td>TRPV6 (ECAC2)</td>
<td>Pancreas, prostate, salivary gland, placenta</td>
</tr>
</tbody>
</table>

Channel properties:
Permeability:
Nonselective cation channel moderately selective for divalent cations, organic cation dyes, aminoglycoside (Eg): Mutation of Asp-646 reduced magnesium permeability.

Desensitization:
Upon activation, TRPV1 shows desensitization. It is a calcium dependent process. Single application of fast acting agent or slow repeated application will cause TRPV1 dependent calcium influx thereby inhibiting feedback signal. Inhibition of calcineurin will stop desensitization.

Regulation:
Heat: Heat gated channel with threshold of 43°C
Voltage: Time dependent activation, positive potential activates while negative potential deactivates TRPV channels.

Vanilloids and lipids: Interacts with vanilloid binding site, vanilloid interaction with TRPV1 depends on specific amino acid residues. Arg-114 in amino and Glu-761 in carboxy terminal plays an important role in ligand binding. Tyr-511 and Ser-512 also plays a valid role in vanilloid mechanisms.

PIP2 is hypothesized to bind to TRPV1 and inhibit the channel hence phospholpase induced PIP2 hydrolysis will lead to TRPV activation. This PIP2 binding is governed by C-terminus in VR.
Protons and cations: A pH of 6-7 causes sensitization of channel to other activators and this in turn is determined by the glutamate residues. Cations govern the TRPV channel based on charge- (Polyvalent >Divalent>Monovalent cations).

Phosphorylation:
By phosphorylating specific residues on the receptor, TRPV1 action can be regulated by protein kinase A and C. Phosphorylation by PK-C causes even room temperature to activate TRPV channels by lowering the threshold for activation.

Others: NGF, SNARE protein mediated exocytosis.

Mechanism of action by vanilloids:
Capsaicin, resinferotoxin (RTX), n-arachidonoyl dopamine (NADA) (agonists) usually bind to vanilloid binding site specifically. Capsacezipine (antagonist) competes with capsaicin for the binding site.

In lipid nanodisc environment, location and orientation of various groups can be studied well in VR. RTX interacts on one side with S1-4V domains and on other side with linker domains. TRPV agonists acts like a molecular glue between linker and S1-4 domains. Many models have been proposed to study
the structure and orientation of TRPV1 and related compounds. Examples: Head down model, pull and contact model by Yang et al. Studies have shown that in resting state, the 4 linker domains that form S6 pore acts as a cuff, one linker domain is active, cuff released and S6 becomes free and thereby activation of channel.

3 distinct states:

I. Closed state (Without agonist)
II. Partial open (Capsaicin bound)
III. Fully open state (RTX, toxins)

Vanilloid receptors in health and disease:\[17\]

I. Pain and inflammation:\[18-32\]

a) TRPV1 and inflammation:
TRPV1 nonselective cation channel highly expressed on sensory neurons can be a promising target for treatment of acute and chronic pain states. TRPV expression is seen in neuronal as well as non-neuronal sites (endothelial cells, keratinocytes, smooth muscle cells).

Intradermal/topical exposure to capsaicin - Intense burning/erythema/hyperalgesia/allodynia
Expression of TRPV1 was found to be increased in painful inflammatory conditions. TRPV1 when blocked led to decreased inflammation induced pain in mice. In pain models, TRPV blocked hyperalgesia.

During inflammation, TRPV1 expressed along the pain pathway (DRG, skin nerve endings, dorsal horn). Most of TRPV expression neurons express inflammatory mediators like CGRP, Substance-P and increased expression of NGF-R. In human studies, increased TRPV expression is found in cases of IBD/GERD/Chronic breast pain, rectal hypersensitivity, faecal incontinence. Hence these findings throw light to the fact that TRPV1 is expressed in most of critical structures of inflammation. Throughout development of VR, CFA induced inflammatory model has been explored widely. Intraplanar injection of CFA in hindpaw (mice) led to thermal hyperalgesia and cold allodynia. In TRPV1 knockout mice, this increased hyperalgesia was attenuated. Other TRPV antagonists like BCTC also reversed thermal hyperalgesia.

b) Osteoarthritis (OA):
OA is shown to involve synovial and joint inflammation as a component in the pathogenesis. Sensory nerve fibres that innervate synovium are afferents that release substance P and CGRP which is found to be increased in neurogenic inflammation. In rat OA models, Increased TRPV1 expression was found in joint capsule. In osteoarthritis, osteochondral bone resorption, inflammation and hypoxia which led to decreased pH may cause TRPV1 activation. Other reasons for neuronal hyperexcitability in OA include peripheral nervous system excitation and tissue hypoxia leading to TRPV1 expression.

TRPV1 antagonist had been evaluated in many preclinical models of OA pain including mono-sodium iodoacetate injection induced OA.

c) Bone cancer:
Challenge faced in tumor growth in bone is that it not only causes pain but also causes other debilitating symptoms like anemia, fractures, reduced mobility, hypercalcemia. Pain in bone cancer may be due to metastasis which is more severe intensity. Studies have shown expression of TRPV1 in afferent nerves that innervate long bones like femur. TRPV1 antagonists decreased bone cancer pain and related syndromes. In mouse model of bone cancer pain, TRPV1 blockers were found to reduce ambulatory as well as ongoing pain related behavior without any noticeable side effects.

d) Visceral pain:
• Urinary tract:
  Neuronal: VR binding in urinary tract was visualized in rat urinary bladder and urethra initially. TRPV1 in IHC studies have been found to be expressed through mucosa/muscularis layer of entire urinary tract in two variations- In mucosa, closely interwined to epithelium and in muscularis over the smooth muscle cells.
  Non-neuronal: Urothelium, interstitial cells of bladder
• GIT:
  Neuronal: TRV1 observed in neuronal fibers in mucosa and submucosa as well as nerves innervating pancreas.
  Non-neuronal: Parietal cells, epithelial cells
e) Migraine:
  Colocalization of TRPV1 with CGRP forms the crux of involvement of TRPV4 in pathogenesis of migraine.
  f) Neuropathic pain:
  TRPV1 agonists almost have reached clinics due to their involvement in neuropathic pain. They have been used clinically for many years to reduce chronic pain associated with diabetic neuropathy. High concentration capsaicin patch is being tried for various types of neuropathic pain including post herpetic neuralgia, diabetic neuropathy. RTX, an ultrapotent vanilloid acts like a molecular scalpel for patients with chronic intractable pain. But one important side effect with capsaicin is the burning sensation, which can be minimized by activity dependent targeting that will affect only hyperactive TRPV1 and spare normal channels.
2. TRPV -Role in CVS and RS:[33-37]
a) CVS:
  TRPV1 is expressed in sensory fibers that innervate myocardium and perivascular plexus. Increased pH of ischemic myocardium and ATP release from damaged cardiac cells will activate TRPV1, which may lead to Bezold-Jarisch reflex.
  Cardioprotective role: Capsaicin afferent release XGRP, NO and has been found to have a cardioprotective role. Studies with neonatal capsaicin treatment reduced sodium excretion predisposing to hypertension. TRPV expression also was found to alter RAS expression.
  Cardiac hypertrophy: calcineurin/NFAT complex regulated by intracellular calcium plays an important role. TRPC3 and C6 are also involved in cardiac hypertrophy apart from TRPV1.

**Atherosclerosis:**

![Diagram of TRPV in atherosclerosis]

**Why TRPV-CVS Target?**
1) Alteration of RAS pathway and reduction of BP
2) CGRP-Promotes separation of endothelin 1 from endothelin receptor- reduced vasoconstriction, reduced BP
3) TRPV1 activation -Reduced renal perfusion pressure, reduced GFR thereby reduced BP
4) Intravascular baroreceptor
5) Reduction in oxidative stress (CGRP mediated)
TRPV and airways:

TRPV1 is expressed along the entire respiratory tract from nose to alveoli, smooth muscle and pulmonary vasculature. In emphysema, increased TRPV1 expression was seen. Inflammation leads to edema and activation of pain fibers, which leads to excitation of neurons that may reduce the threshold for activation of TRPV receptor. TRPV channels may be expressed in airways that do not usually express them and only in cases of airway hyperactivity. TRPV1 agonists was found to cause alveolar cell death. TRPV4 is a thermosensor and has a role in mucociliary clearance. TRPV1 role is explored in cough, heart failure associated with pulmonary edema and airway hyperactivity in asthma.

3. Role in bladder disorders:

TRPV1 knockout mice showed features of inefficient voiding and increased urinary contractions. Intravesical vanilloids were found to be a therapeutic strategy for treatment of detrusor overactivity and cystitis. TRPV1 is expressed in neuronal urothelium and has a role in micturition reflex. TRPV1 antagonists blocks detrusor overactivity. TRPV4 is abundantly expressed in urothelial associated stretch receptors.

TRPV1 agonists in neurogenic detrusor overactivity:

Activation of TRPV1 agonists caused prolonged desensitization which affects neuropeptide release and thereby reduce symptoms. Side effects seen are bladder pain and neurotoxicity. Number of TRPV1 positive nerve fibers correlate with pain sensation. Inhibition of TRPV1 reduced symptoms of cystitis.

4. GIT:

VR1 is expressed in the myenteric plexus, muscle fibers and on primary afferent neurons as mentioned above. With wide range of preclinical studies and established models, VR

Figure 3: TRPV and airways

Figure 4: TRPV in IBD

have been therapeutically implicated in following - gastroprotection, IBD, IBS and ulcer. Studies have also proven expression of VR1 in pathogenesis of Hirschsprung disease.
Figure 5: TRPV in gastroprotection

Figure 6: TRPV in gastric ulcer
5. Skin and appendages

TRPV1 is expressed in neuronal as well as non-neuronal part of skin. They play an important role in normal skin as well as pathophysiology of various cutaneous disorders. Function of TRPV1 involves skin and hair growth and differentiation, immunological role and pathophysiological role.

**TRPV1 in skin:**

a. **Protective role:** Keratinocyte differentiation forms one of the major components of skin barrier. Agents that modify intracellular calcium will affect keratinocyte differentiation that affects epidermal barrier. Studies have shown that activation of TRPV1 induced by application of capsaicin caused disruption of skin barrier and antagonism of TRPV1 accelerates this repair.

b. **Hair follicles and keratinocytes- anti-proliferative property:**
TRPV1 expression increases levels of hair follicle inhibitory factor and pro-inflammatory mediators and decreases level of hair growth promoters, reduction in hair follicle cycle. TRPV1 antagonism may be tried in alopecia, while agonist approaches are tried for hirsutism.

**Inflammatory skin disorders:**
Studies have shown that TRPV1 activation of keratinocytes with capsaicin increased COX2, pro-inflammatory mediators and upregulation of MMP. In mice model of psoriasis, topical capsaicin decreased expression of inflammatory mediators hence played a role in skin inflammation.

**Cutaneous immunological functions:**
Capsaicin stimulation by activating TRPV1 caused local intracutaneous release of neuropeptides and activation of skin cells located nearby to nerve endings leading to release of proinflammatory mediators and so called “inflammatory soup” causing vasodilatation and edema but still role of TRPV in neurogenic inflammation is contradictory. TRPV3 and 4 also play an important role in skin. TRPV3 co-expression with EGFR and TGF and others signal molecules that form the epidermal barrier.

Olmsted syndrome- Gain of function mutation of trpv3 gene characterized by hyperkeratosis.

6. CNS

**Physiological role:** Changes in level of endogenous vanilloids activates neuronal TRPV1 which plays a role in modulating synaptic activity.
• TRPV1 - expressed in hippocampus and cortex
• TRPVV2 expressed in hypothalamus, hippocampus, globus pallidus and putamen
• TRPV3- expressed in cerebellum
• TRPV4- expressed in cortex
• TTRPV5— expressed in cortex/midbrain

Diseases in CNS:

A. Epilepsy: In both in vitro and in vivo models of epilepsy, TRPV1 agonist showed a protective role by reducing brain damage in Aβ induced Alzheimer’s disease, reduced apoptosis and inhibited oxidative stress and increased antioxidants. TRPV1 blockers are found to suppress seizures following traditional models of seizures. Capsaicin also suppressed kainic acid induced seizures.

B. Stroke: TRP channels are found to play an important role as they are associated with calcium induced neuronal death by their interplay with other NMDA and glutamate receptors. In transient MCAO model of TRPV1 KO mice, capsezepine stopped neurologic and motor deficit and improved infarct size.

Alzheimer’s disease:
Accumulation of Aβ plaques in brain causes ROS generation and inflammation and dysregulates calcium ion homeostasis causing neuronal death. TRPV1 agonist improved neuronal damage by reducing oxidative stress and Tau phosphorylation. Administration of TRPV1 agonist intracerebroventricular in STZ model improved oxidative stress.

Parkinson’s disorder:
TRPV1 activation prevented dopaminergic neuronal degeneration and enhances the behavioural symptoms and also reduced oxidative states in studies with MPP lesion model of PD in rat, capsaicin reduced degeneration of dopaminergic neuron.

Migraine:
Vanilloid TRPV1 antagonists are investigated in clinical trials for treatment of acute migraine. TRPV1 are located on small and medium sized neurons in DRG and activated by heat/capsaicin/protons. Intravenous capsaicin increased release of proinflammatory neuropeptides CGRP and substance P, which causes plasma protein extravasation activates TRPV1 and in turn causes dilation of blood vessels leading to migraine.

Role of TRPV1 is explored in other behavioural disorders including psychosis, depression due to its property of affecting neuronal plasticity.

Other therapeutic roles: TRPV channels are also implicated widely in DM and obesity (TRPV1 AND TRPV4), Vit D metabolism (TRPV3), Cancer states (glioma andprostate cancer), regulation of taste sensation, regulation of inner ear vasculature and protective role in sepsis, ischemia and reperfusion injury proves that TRPV is more than just a pain sensor. Other important roles:[54-56]

- Role in thermoregulation:
TRPV play an important role in detection of external thermal stimuli. Thermo TRPs mainly TRPV1-4 expressed in sensory nerve endings and skin that can respond to different temperatures thresholds. TRPV1-sensitive at >42°C
TRPV2->52°C
TRPV3->33°C
TRPV4->27°C-42°C

TRPV knockout studies have shown impaired thermal hyperalgesia and thermal avoidance. Recently evidence suggests the possibility of non-thermal chemosensors in TRPV family.

- Role in calcium homeostasis:
TRPV1, 2, 3 and 4 are thermosensitive while TRPV5 and 6 are highly sensitive for calcium. Involved in many calcium sensor pathways thereby regulating many disorders as discussed above.

- Role in endoplasmic reticulum:
Two VR pools exist broadly- Plasma membrane (role in calcium signaling) and ER(role in synaptic transmission). TRPV1 activation increases cytosolic calcium as discussed previously and brings about the effects. Studies have shown that 85-90 percent of functional TRPV1 expressed on ER membrane. TRPV1 activation by activation of EIF2α kinases and phosphorylation of EIF2α results in cytotoxicity.
Overview of vanilloid receptor agonists and antagonists:[57-63]

**Agonists:**
Existing agonists include capsaicin, a pungent component of peppers that was later identified to be a type of homo-vanillyl compound that acts as a potent TRPV1 agonist which increased intracellular calcium concentrations in sensory neurons. RTX another ultrapotent vanilloid is also a well-known agonist at TRPV1 which binds with high affinity. Main advantage is broad mechanistic effect related to desensitization while disadvantage is most of existing agonists evokes pain upon administration so need of local anesthetic treatment along with it may potentiate side effects and also causes neurotoxicity. Recently injectable capsaicin formulations are being assessed for neuropathic pain.

<table>
<thead>
<tr>
<th>Table 2: New agonist molecules under development</th>
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</tr>
<tr>
<td>ALGRX-4975</td>
</tr>
<tr>
<td>WN-1001</td>
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<tr>
<td>NGX-4010</td>
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**Antagonists:**
Capsazepine is a competitive antagonist for TRPV1 and structurally similar to capsaicin. It competes with capsaicin for binding and inhibits capsaicin mediated activity and displaces RTX from binding site and also found to inhibit both heat and proton mediated TRPV activation. Ruthenium red is another functional blocker of TRPV channels.
Rapid onset of action and no pain evoked after administration makes them a bit superior in the clinical world when compared to TRPV agonists but side effects need to be explored more.

<table>
<thead>
<tr>
<th>Table 3: New antagonist molecules under development</th>
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<tbody>
<tr>
<td>Agonists</td>
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<tr>
<td>JTS-693</td>
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<tr>
<td>MK-2295</td>
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<td>SB-705498</td>
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Anandamide and vanilloid receptors:[64]
Anandamide, a potential activator of cannabinoid receptor after many years of its discovery was found to have a role in VR thereby referring to the molecule as endovanilloid. Potency and efficacy of anandamide at VR is tissue specific and action is controlled by local metabolism and metabolites of anandamide also found to have a role in TRPV channel response. Role of anandamide is being explored in temperature regulation, obesity and also in the well-known field of analgesics.

Challenges faced: [1,17]

Identifying and validating new drug binding sites on TRPV1 will require more knowledge of how channel works with respect to its protein structure which may play a key role in more clearly concluding its role in inflammation.
Main challenge in TRPV1 modulation drugs will be to design drugs that can distinguish between physiological and pathological actions. the widespread distribution and still many unknown functions of TRPV1 indeed poses a threat to any TRPV molecule that needs to enter clinical realm.

**CONCLUSION:**
Despite the intensified and complex efforts in identifying the role of VR in Drug discovery and increased number of VR agonists and antagonists entering clinical trials, results have not been obtained from any proof of concept studies even in the area of well-known analgesia. Clinical data may help to further assess the safety and efficacy and maybe clinical validity of molecules acting on TRPV and hence may shed light on role of TRPV in clinical practice.

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