B'SYS GmbH

TRP Channels

Specification Sheet

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1 INTRODUCTION

Transient receptor potential channels, also called TRP channels, are a superfamily of ion channels occurring in cell membranes that are involved in various types of sensory reception, including thermoreception, chemoreception, mechanoreception, and photoreception. Their responses to various stimuli are manifested through their functions as ion channels, regulating the flow of ions, such as potassium, calcium, and sodium, into or out of cells. Ion flux can lead to cell membrane depolarization, which leads to an action potential.

The major groups of TRP channels include TRPM (melastatin), TRPV (vanilloid), TRPC (canonical), TRPP (polycystin), TRPML (mucolipin), and TRPA (subfamily A). TRPM, TRPA, and TRPV channels can respond to changes in temperature, with TRPM and TRPA known to respond to cold and TRPV known to respond to warmth, noxious heat, and pain. TRPV channels have been identified on sensory neurons and on epithelial cells, and TRPM channels are primarily expressed on C-fibres in peripheral nerves. TRPC channels are expressed primarily on smooth muscle and heart cells and appear to regulate certain responses in the central nervous system and in the vasculature. TRPP channels are expressed on kidney cells and on the cells of the retina and may play a role in controlling the responses of cilia to fluid flow in the renal epithelium. TRPM channels are capable of distinguishing among tastes, including sweet, bitter, and umami (meaty).

2 TRP-CHANNELS AT B'SYS

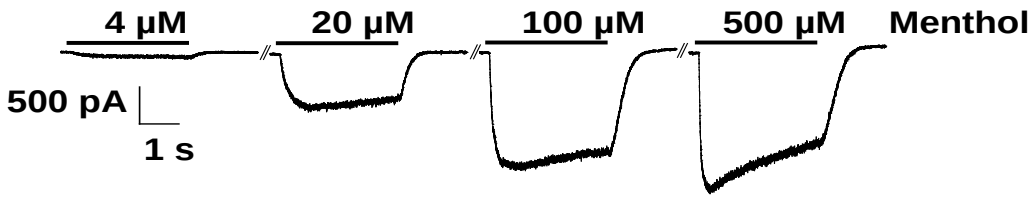
B'SYS offers the following TRP Channel services and cell lines:

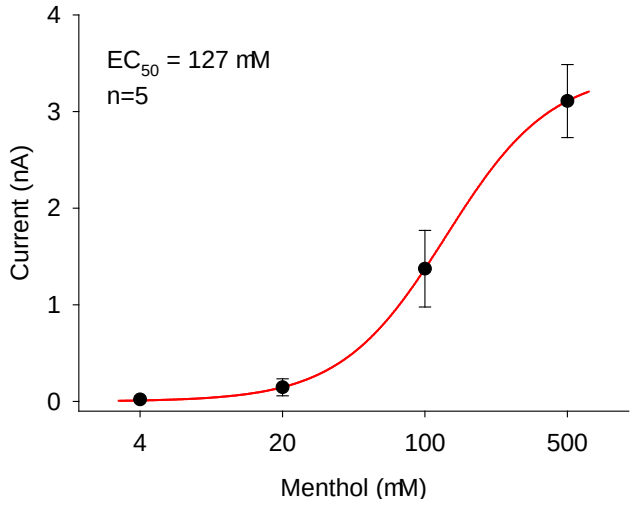
TRP-Channel	**Service**	**Cell Line**
TRPM8	Fluorescence (FLEX station) automated and manual patch-clamp	CHO / HEK293
TRPV1	Fluorescence (FLEX station) automated and manual patch-clamp	CHO
TRPV2	manual patch-clamp	HEK293
TRPV3	manual patch-clamp	CHO / HEK293
TRPV4	manual patch-clamp	HEK293
TRPA1	manual patch-clamp	HEK293

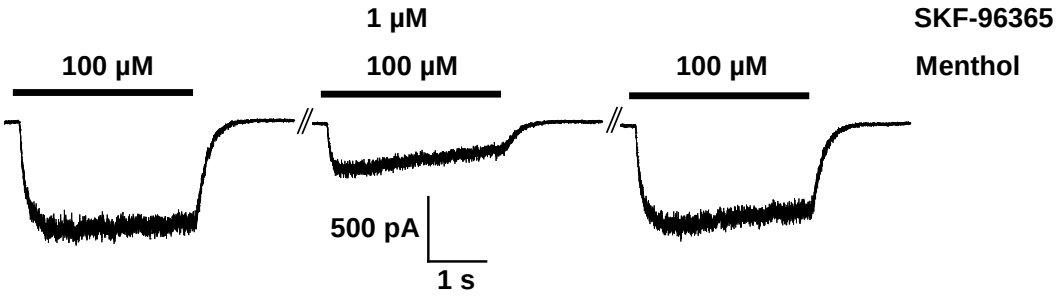
3 VALIDATION OF TRP CHANNELS

3.1 TRPM8

The cold and menthol receptor, TRPM8, is the predominant thermoceptor for cellular and behavioral responses to cold temperatures. Unlike other thermally-gated TRP channels which are activated at either innocuous or noxious temperatures, TRPM8 provides perception of both pleasantly cool and painfully cold. In addition to this diversity in sensory signaling, TRPM8 has an emerging role in a variety of biological systems, including thermoregulation, cancer, bladder function, and asthma.

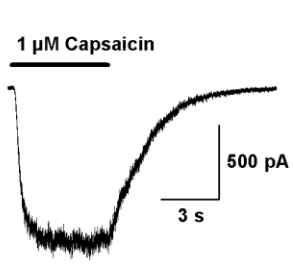


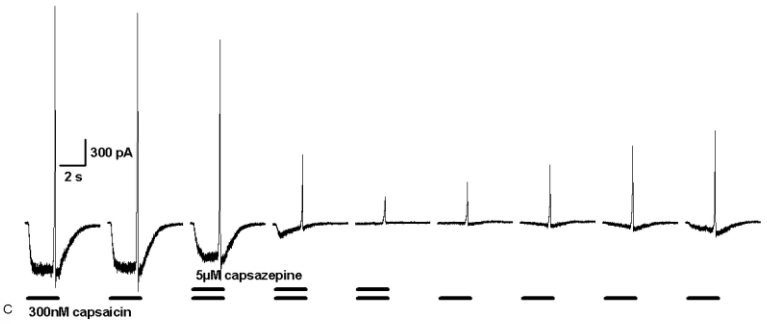


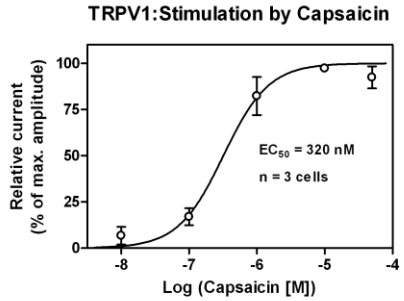


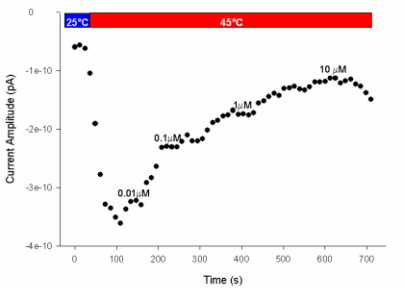
3.2 TRPV1

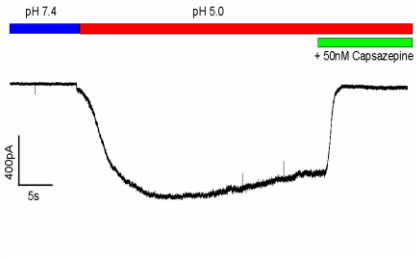
TRPV1 is activated by a wide variety of exogenous and endogenous physical and chemical stimuli. The best-known activators of TRPV1 are: temperature greater than 43°C (109°F); acidic conditions; capsaicin, the irritating compound in hot chilli peppers; allyl isothiocyanate, the pungent compound in mustard and wasabi. The activation of TRPV1 leads to a painful, burning sensation. Its endogenous activators include: low pH (acidic conditions), the endocannabinoid anandamide, and N-arachidonoyl-dopamine. TRPV1 receptors are found mainly in the nociceptive neurons of the peripheral nervous system, but they have also been described in many other tissues, including the central nervous system.

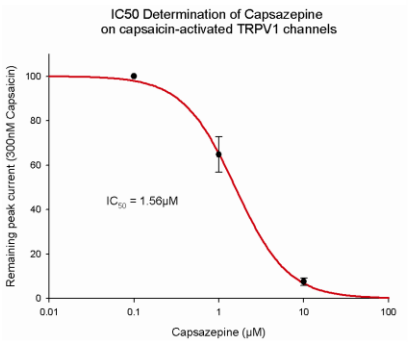


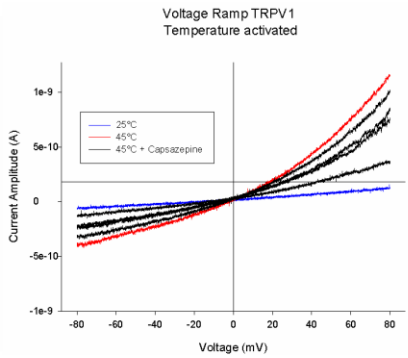


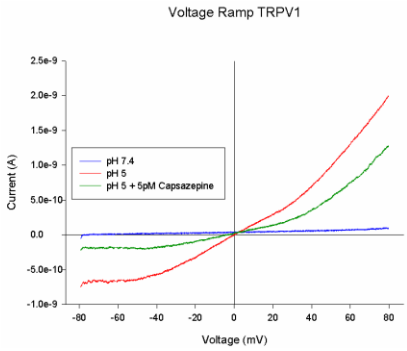






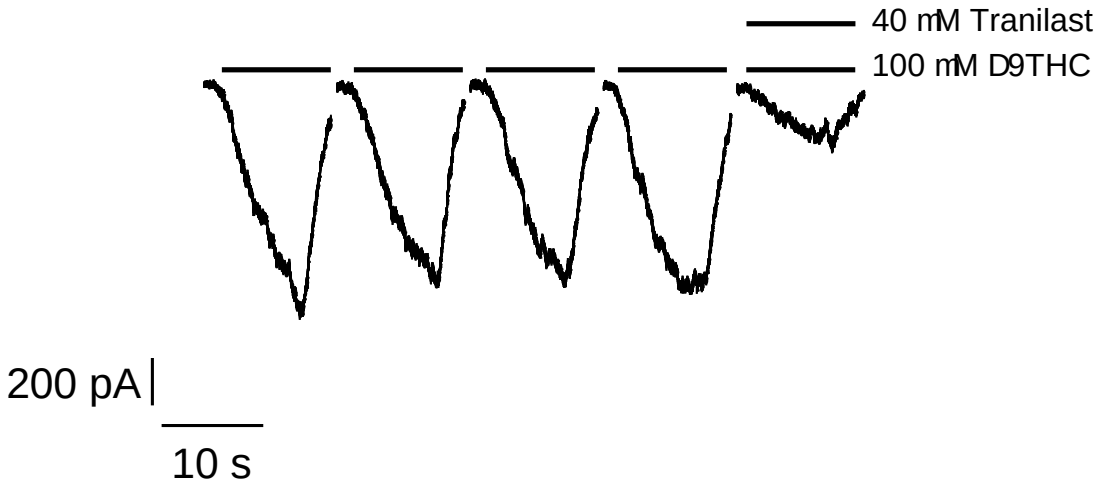






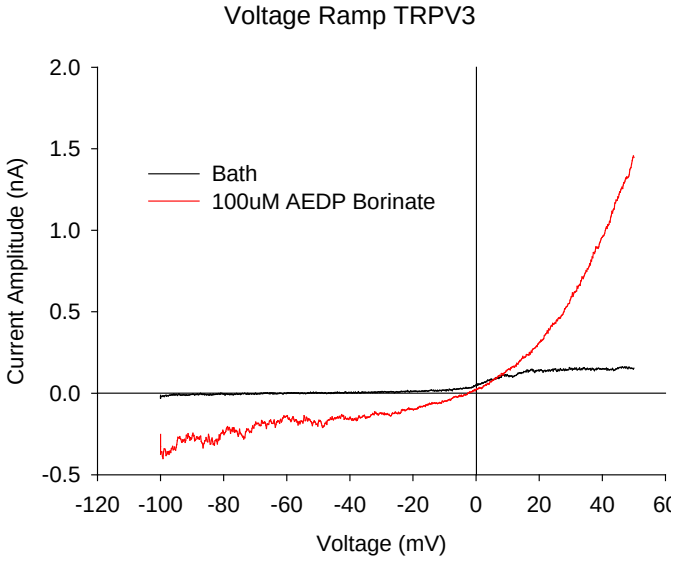
3.3 TRPV2

One of the least characterized members of the TRP subfamily is TRPV2. Although initially characterized as a noxious heat sensor, TRPV2 now seems to have little to do with temperature sensing but a much more complex physiological profile. The most reliable pharmacological modulators for TRPV2 are probenecid and cannabidiol, as agonists, which are also known to activate/inhibit other TRP channels (e.g. TRPV1, TRPA1, TRPM8. Regarding inhibition, tranilast has been identified, so far, as a TRPV2-specific antagonist.



3.4 TRPV3

The vanilloid transient receptor potential channel TRPV3 differs in several aspects from other members of the TRPV subfamily. This Ca^{2+}, ATP and calmodulin regulated channel constitutes a target for many natural compounds and has a unique expression pattern as the most prominent and important TRP channel in keratinocytes of the skin. Although TRPV3 is considered as a thermosensitive channel, its function as a thermosensor in the skin is challenged. Nevertheless, it plays important roles in other skin functions such as cutaneous sensations, hair development and barrier function.

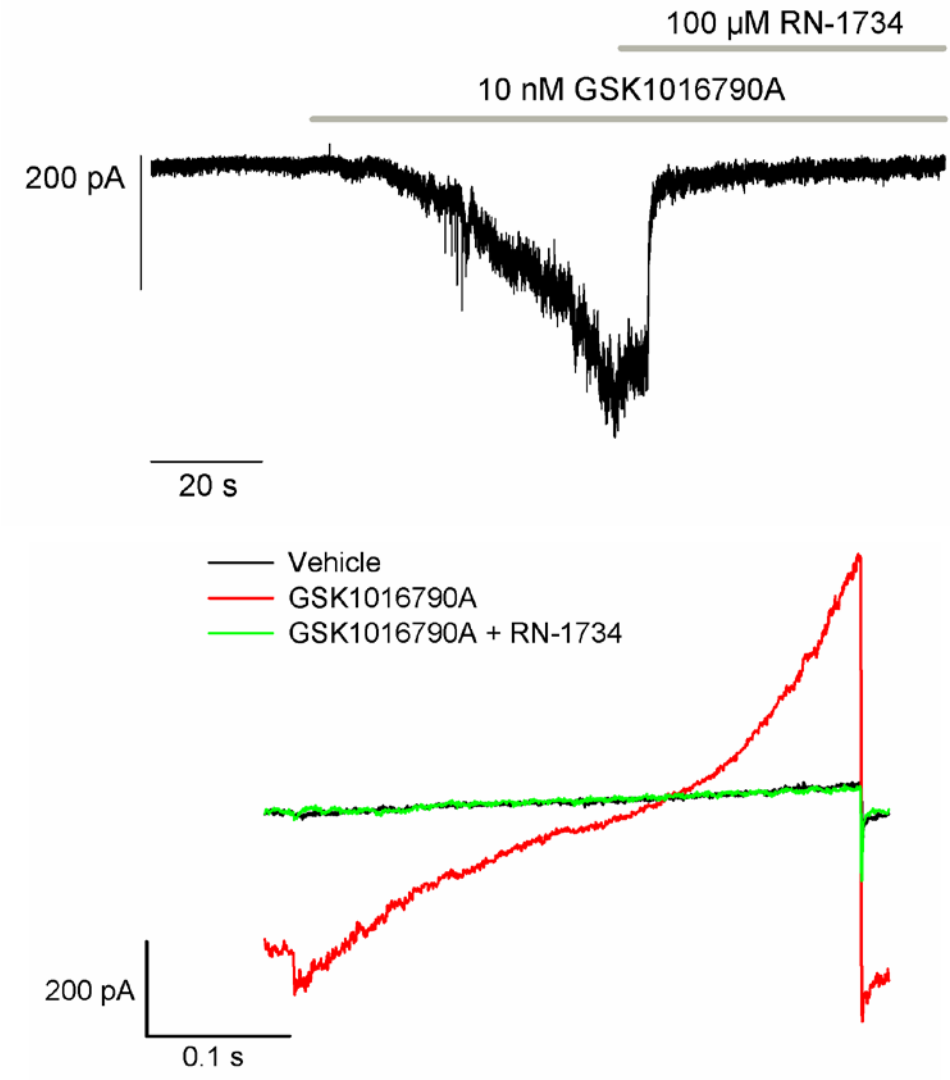


3.5 TRPV4

TRPV4 is widely expressed. TRPV4 is strongly expressed in kidney. In addition, the human isoform has been cloned from a hypothalamus library and the chicken variant from an auditory epithelium library [12].

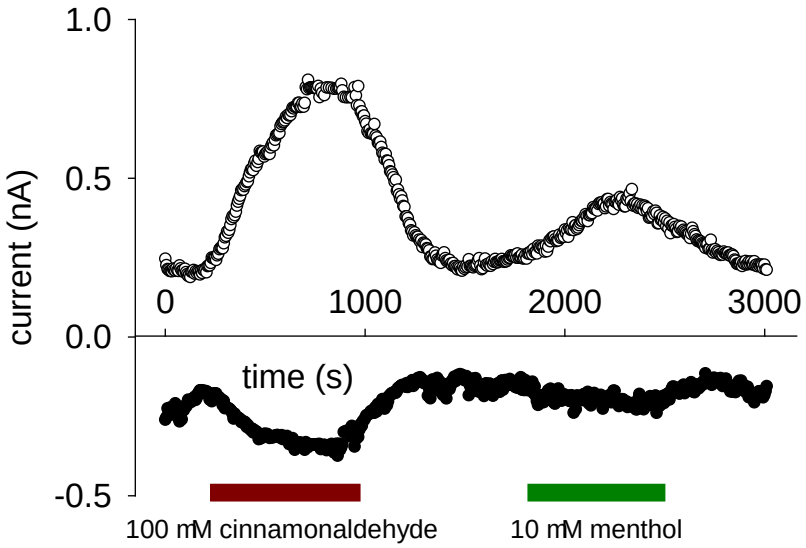
TRPV4 is highly sensitive to changes in extracellular osmolarity around the normal osmolarity of body fluids. Reductions in the extracellular osmolarity result in increases in $[Ca^{2+}]i$ and membrane currents, whereas osmolarities above 300 mosmol l^{-1} decrease both $[Ca^{2+}]i$ and currents. The involvement of TRPV4 in responses to cell swelling and its localization in tissues like the inner ear, sensory neurons, and endothelial cells that are known to express mechanosensitive channels raise the question of whether TRPV4 is a mechanosensitive channel. A very important finding for TRPV4 was the identification of phorbol ester derivatives as channel activators. TRPV4 was found to be activated by 4α-phorbol ester derivatives with EC50 values around 0.2 µM for 4α-phorbol dide-canoate (4αPDD). Responses of TRPV4 to warm temperatures and its expression in sensory neurons, keratinocytes, and in the hypothalamus indicate further a role for TRPV4 in thermosensation and thermoregulation.

Recently the TRPV4 agonist GSK1016790A (300 fold more potent than 4αPDD), which was used as a valuable tool in investigating the role of TRPV4 in the urinary bladder, was identified.



TRPA1

In mammals, TRPA1 is the sole member of the TRPA gene subfamily. Recent reports identified TRPA1 as a target for the noxious and inflammatory irritant mustard oil in peripheral sensory neurons, implicating a functional role in pain and neurogenic inflammation. In addition to mustard oil, TRPA1 is activated by other pungent plant products such as cinnamaldehyde, eugenol, gingerol, and methyl salicylate.



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