Ph.D. Thesis

EXPRESSION AND ROLE OF TRPV1 AND TRPA1 ION CHANNELS AND SENSORY NEUROPEPTIDES IN INFLAMMATORY PROCESSES OF THE SKIN AND THE COLON

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INTRODUCTION

The TRPV1 receptor

It was discovered in Hungary in the 1950-60's that capsaicin, the pungent compound of hot peppers selectively activates and in repeated doses damages a heat sensitive subgroup of nociceptive nerve terminals [1,2]. The concept of capsaicin acting on a specific membrane receptor was also conceived in Hungary in the following decade [3]. The receptor has been known as the Transient Receptor Potential Vanilloid 1 since its cloning in 1997 [4]. The rat Trpv1 cDNA codes for a 95 kDa non-selective cation channel subunit highly expressed by small diameter sensory neurons of dorsal root (DRG), trigeminal and vagal ganglia. The TRPV1 subunit has six transmembrane domains with extensive N- and C-terminal regions. The subunits form tetrameric and/or heteromeric channel complexes.

Besides capsaicin, TRPV1 is activated by noxious heat (>43 °C), protons (pH <6,0), exogenous vanilloids, and various inflammatory and nociceptive endogenous molecules (e. g. N-arachidonoil-dopamin: NADA, lipoxigenase products, anandamid), or sensitized by bradykinin, adenosine-triphosphate: ATP, nerve growth factor: NGF, etc [5,6]. Exogenous vanilloid agonists including capsaicin and its ultrapotent analogue resiniferatoxin (RTX) act on the intracellular and transmembrane regions of the receptor in a dose-dependent manner [7]. Ultrapotency of RTX is explained by its chemical structure [8]**.** TRPV1 activation generates action potential resulting in sensory activation and nociception. On one hand, it transmits different sensory modalities (pain, itch, thermosensation, etc.) as an *afferent* function. On the other hand, activation of capsaicin-sensitive sensoy nerve fibres leads to the release of various, mainly proinflammatory neuropeptides as a local *efferent* function [9,10]. These neuropeptides (substance P, neurokinin A: NKA, neurokinin B: NKB, calcitonin gene related polypeptide: CGRP) cause dilatation of arterioles, release of plasma proteins from venules, and activation of inflammatory cells [11]. This results in neurogenic inflammation that plays a role in several inflammatory diseases, such as asthma bronchiale, allergic rhinitis, conjunctivitis and dermatitis, ekczema, rheumatoid arthritis, migraine, inflammatory bowel diseases [12–14]. It has been demonstrated by our research group that antiinflammatory somatostatin is also relased form activated sensory nerve endings distributed systemically as a *sensocrine* effect [10,15]**.**

TRPV1 desensitization

Capsaicin not only selectively activates but also desensitizes C-polymodial nociceptors in long-term application or in high doses [1,10]**.** This *chemoanalgesia* is used as an experimental method to investigate the lack of functional TRPV1 [10]. In systemic TRPV1 desensitization experiments RTX is preferred since it is better tolerated by animals [8]. RTX is able to induce desensitization by 1000 fold efficiency: the systemic RTX dosage is 150-200 µg/kg, while that of capsaicin is in the range of 150-200 mg/kg [1,8,16–18]. Upon activation, mainly Ca^{2+} ions pass through the channel's pore leading to the increase of intracellular Ca^{2+} concentration and membrane depolarization. Capsaicin treatment applied locally or systemically induces a long-lasting but reversible analgesia; repeated or large doses can physically destroy the sensory nerve endings [1,10,19]. Animals desensitized by capsaicin do not respond with protective reflexes or neurogenic inflammation when treated with noxious chemical substances. This points to the depletion of inflammatory mediators (substance P, NKA, CGRP) from nociceptive nerve endings. Systemic RTX pretreatment is applied as a selective pharmacological method to desensitize TRPV1-positive sensory nerve endings in animal experiments investigating the role of sensory fibres in inflammation (neurogenic component) [10]. The discovery of non-neuronal TRPV1 channels raises the question: can RTX desensitization (after having been in use for decades) can still be viewed as a selective experimental method that destroys only sensory neurons but does not affect non-neuronal cells? Since TRPV1 antagonists for the treatment of severe pain have not yet passed through phase II clinical trials due to their side effects (chiefly because of the elevation of noxious heat threshold), attention has been directed toward therapeutical desensitization of capsaicin-sensitive nerve endings (e. g. Qutenza transdermal patch).

The TRPA1 receptor

The Transient Receptor Potential Ankyrin 1 (TRPA1) is similar to TRPV1 in terms of molecular structure, function and localization [20]**.** TRPA1 and TRPV1 are extensively coexpressed in a subpopulation of peptidergic, afferent Aδ- and C-fibers whose cell bodies lie in dorsal, trigeminal and vagal ganglia (ggl. jugulare, ggl. nodosum) [21–24]. 30-50 % of TRPV1-expressing sensory neurons contain TRPA1 while the latter is rarely found in neurons without TRPV1 [25,26]. TRPV1 has been detected in various brain regions [27–30] and TRPA1 is proposed to be present [29,31,32]. TRPA1 and TRPV1 is generally colocalized in non-neuronal cells, as well (e. g. epithelium, keratinocytes) [6]. Cellular functions of TRPA1 as a

non-selective Ca^{2+} channel range from sensory roles to maintaining homeostasis. The receptor can be activated by cold temperature (<17 °C), mechanical stimuli, various electrophilic, irritant, spicy chemicals, many found in the human diet (cinnamaldehyde, menthol, allyl-isothiocyanate, allicin, etc.) [33]. The receptor can be activated or sensitized by endogenous agonists released during inflammation, tissue damage, oxidative stress [34–37]. The TRPA1 receptor plays a key role in acute and chronic pain and inflammation based on its localization and functional properties. Its pathophysiological significance and role as a potential drug target have been considered in inflammatory diseases of the airways, the cardiovascular system and the gut [33].

PACAP

The capsaicin-sensitive nerve endings express not only proinflammatory neuropeptides but also antiinflammatory ones, for example, the hypophysis adenylate cyclase activating polypeptide or PACAP. The molecule has two forms: PACAP-27 és PACAP-38, chiefly the latter is represented in mammals [38]. PACAP is the most conserved member of the vasoactive intestinal peptide/secretin/glucagon superfamily [38]. The specific receptor of PACAP is PAC1 that can be coupled to both G_s and G_q proteins, the former way activating the adenylate cyclase (AC) pathway, the latter way the phospholipase C (PLC) pathway. The VPAC1 and VPAC2 receptors bind similarly PACAP and VIP and activate adenylate cyclase leading to enhanced cAMP production [42]. PACAP and its receptors are widespread throughout the body [38] consequently playing a role in several physiological and pathophysiological processes. The peptide is basically known as an antiinflammatory, neuroprotective agent. Nevertheless, it may mediate pathophysiological processes toward inflammation and nociception as well by acting on various cells, receptor variants/types, and yet not identified new splice variants [38,41,42,45–53]. Our research group has recently proven the release of PACAP-38 *in vitro* from stimulated peripheral endings of capsaicin-sensitive afferents [54] and its systemic *in vivo* release [46]. The localiztaion of PACAP in human skin has been described in dermal nerve fibers, hair follicles and blood vessels and sebocytes near the dermal-epidermal barrier [38] and the high affinity PAC1 receptor was also detected. PACAP and PAC1 upregulation were observed in psoriasis patients which points to the role of PACAP in inflammatory mechanisms of the skin [55].

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are prevalent disorders of the intestine, such as ulcerative colitis (UC) and Crohn disease. UC only affects the colon, Crohn's disease affects the entire gastrointestinal tract, but most often the distal small intestine, ileum and colon are affected by the chronic inflammatory state. The main symptomes of IBD are abdominal pain, diarrhea, gastrointestinal bleeding and weight loss [56]. One of the most frequently used non-genetic colitis murine models is the one elicited by dextrane-sulphate-sodium (DSS). DSS chemically damages the epithelial mucosa (barrier), induces colonic inflammation and ulcers leading to progressive loss of Lieberkühn crypts, alteration of microflora and accumulation of inflammatory cells [57,58]. IBD is a painful and debilitating disease of the GI track causing deteriorating life quality and may become life-threataning. Available immune suppressive therapies have serious side effects. This poses a driving force to understand the complex pathophysiological mechanisms, identify key mediators and find new therapeutic targets [59]. Capsaicin-sensitive nerve fibers [10,60] densly innervate the gastrointestinal tract [61,62] whose activation releases proinflammatory neuropeptides (substance P, NKA, CGRP) [63]. TRPA1 is located in different systems of the GI tract: *extrinsic* primary afferent neurons, *intrinsic* enteric neurons, and endocrine and epithelial cells of the mucosa [20,61,62]. TRPA1 acts as an environmental chemosensor in the gut lumen and modulates gastrointestinal functions: nociception, gastric tone, satiety induced by spicy diet, motility and secretion [20]. TRPA1 activation leads to the release of inflammatory neuropeptides from sensory nerve endings and provokes neurogenic inflammation [64]. Substance P induces and maintains colitis in the DSS model and in patients with ulcerative colitis [65,67,68]. Activation of TRPA1 induces substance P release, however, TRPA1 has been found to be prinflammatory, antiinflammatory or without any effect in murine colitis models [65,69–71]. TRPA1 activation releases CGRP with a protective role in colonic inflammation [65,66]. Our group has demonstrated that activation of sensory TRPA1 leads to the release of antiinflammatory peptides, e. g. somatostatin that provokes a counterregulatory „sensocrine" effect [72,73]. The field has become even more complex by the discovery of non-neuronal TRPA1 channels whose physiological roles are not yet understood [6].

AIMS

1. Does capsaicin/RTX desensitization damage extraneuronal TRPV1 channels?

In animal models of pain and inflammation, the role of sensory neurons is often studied by applying capsaicin or RTX desensitization. We aimed to investigate wether the experimental method is truly selective for TRPV1-positive sensory neurons without damaging extraneuronal TRPV1 receptors? We set out to detect gene and protein expression changes in skin and buccal mucosa of RTX-desensitized and surgically denervated rats as controls.

2. What is the role of TRPV1-PACAP connections in capsaicin-induced skin inflammation?

It has been known that *a)* the specific TRPV1 agonist capsaicin induces neurogenic inflammation in the skin, and *b)* PACAP plays a role in acute vasodilatation during inflammatory processes. However, it has not been known if there is a connection between the two, and what role do PACAP and its specific receptor PAC1 play in this process. Therefore we aimed to investigate the expression of PACAP and PAC1R at the mRNA and protein levels in dorsal and plantar paw skin and back skin in neurogenic inflammation induced by capsaicin and in celullar inflammation evoked by Complete Freund's Adjuvant (CFA) in Trpv1 and PACAP (Adcyap1) KO mice.

3. What is the role of TRPA1 in inflammatory bowel diseases?

First we aimed to investigate the localization of TRPA1 and TRPV1 receptors in the intact and inflamed murine and human colon, with an emphasis on their extraneuronal occurence. Secondly, we set out to examine the receptor's role in Trpa1 KO mice in the DSS-colitis model. To investigate the underlying mechanisms we detected the expression of local neuropeptide pathways and cytokines/chemokines in the distal colon.

EXPERIMENTAL MODELS AND METHODS

Surgical denervation in rats

Surgical denervation (incision of *sciatic* and *saphenous* nerve at the level of the thigh, under sodium-pentobarbital anesthesia) was performed on the hind legs of 6 male Wistar rats (weight: appr. 300 g) which resulted in the degeneration of nerve fibers. The animals were sacrificed five days later. The dorsal (hairy) and plantar (hairless) skin of denervated and control hind legs were excised and cut into two pieces for qPCR and immunohistochemistry.

RTX desensitization in rats

Five male rats were desensitized by applying 30, 70, és 100 µg/body weight kg RTX *s.c.* on three consecutive days [74]. Five animals received physiological saline solution. Animals were sacrificed two weeks later. Five days later the animals were sacrificed. Dorsal (hairy) and plantar skin of hind legs and buccal tissue were excised and cut into two pieces for qPCR and immunohistochemistry.

Induction of acute skin inflammation in mice

Experiments were performed on male CD1 mice (25-35g) and PACAP (Adcyap1) gene-deficient mice based on the CD1 strain, and on C57Bl/6 and Trpv1 KO mice. Anesthesia was performed by ketamin-xylazin (100 mg/kg ketamin *i.p.*) then animals were terminated and skin samples were excised. Tissue samples were cut into three pieces, one was placed into RNAlater for molecular biology studies, another one freezed in -20˚C for radioimmunassay, a third fixed in formaldehyde. Neurogenic inflammation was induced with 50 µl capsaicin (100 µg/ml, i. p. injection). A dominantly cellular inflammation was induced with complete Freund's adjuvant (CFA; heat-killed *Mycobacterium tuberculosis* in a water-in-oil emulsion; 50 µl, 1 mg/ml) administered into the left hind leg. Respective solvents were injected into contralateral legs. Mice were terminated 24 hours after capsaicin or CFA treatment. Skin samples from dorsal and ventral hind paws and back skin, and from hypophysis and hypothalamus as controls. To measure paw oedema evoked by capsaicin and CFA paw volume was detected by a plethismometer (Ugo Basile Type 7140) several times before and after inducing inflammation. Extent of oedema was expressed as a percentage of the initial control (n=6-8 / goup) [75].

Induction of colitis in mice

Chronic colonic inflammation (colitis) was evoked in WT and Trpa1 KO male mice by administering 2% DSS in drinking water for 10 days. WT and KO animals were divided randomly into water-drinking control groups (1 control group/genotype, n=5/group) and DSS-receiving groups (n=9 WT; n=9 KO). 3-3 WT and KO mice were randomly selected to be terminated on days 3, 7 and 10 in ketamin-xylazin deep anesthesia after fasting overnight. Distal third of the colon was excised for further examinations. Disease Activity Index: scoring of clinical symptoms of colitis (weight change, fecal consistency, fecal blood content) on days 1-10 of the treatment. Fecal blood content was determined with the Hemocare test. The scores of the 3 parameters were averaged for each mice to calculate the Disease Activity Index, DAI [76]. Histology: distal colon samples were fixed in 40 mg/ml buffered formaldehyde, sections were made (5 μm), then hematoxylin-eosin staining was performed. Digital microphotos were taken using an Olympus BX51 microscope and Olympus DP50 camera. Inflammatory signs were evaluated and scored by an expert pathologist [76] not participating in the study.

Clinical samples

Colon biopsies were carried out in the 1st Department of Internal Medicine of the University of Pécs in three groups of patients: *1.* non-inflammatory colon disease or check-up examination participant (n=5); *2.* colon tumor (polypus coli, adenocarcinoma, n=8); *3.* ulcerative colitis or Crohn's disease (n=10). Samples were stored in RNALater in -80˚C for qPCR. Samples for immunohistochemistry were stored in formaldehyde.

mRNA expression

Tissue samples were homogenized in 1 ml TRI Reagent and total RNA was isolated according to the manufacturer's instructions. The quantity and purity of the isolated total RNA was determined using a Nanodrop ND-1000 Spectrophotometer. 1 μg total RNA was transcribed into cDNA by reverse transcription. Gene expression was detected in cDNA samples either by legacy PCR followed by gel-based detection using ethidium bromid and UV light (primers specific for Gapdh, PACAP/Adcyap1, PAC1R/Adcyap1r1) or quantitative PCR (primers or TaqMan probes specific for TRPV1, TRPA1, TNFα, Il-1rn, M-csf, BLC/Cxcl13, somatostatin, Tac1, Tacr1, Tac3, GAPDH, GUSB, Hprt1).

Histology, immunohistochemistry

Paw skin samples were fixed in 4% paraformaldehyde. Hematoxylin-eosin staining was applied for histological evaluation. *Rat denervation*: sections were incubated in 1:1000 dilution with anti-TRPV1 antibody for 1 hour, then with Envision system anti-rabbit secondary antibody conjugated with horseradish peroxidase, and finally immunolocalization of TRPV1 receptors was developed by diaminobenzidine (DAB) for 10 minutes, nuclei staining was performed with hematoxylin. Immunopositivity was determined with semiquantitative scoring by an expert pathologist not included in the experiments. Image Pro Plus 4.5 software was used to analyze the number of TRPV1 positive keratinocytes. *Skin inflammation:* sections were incubated with anti-PAC1 antibody raised in rabbit (1:100), with the respective Alexa Fluor ‘‘568’’ secondary antibody (1:1000). Digital photos were taken with a Nikon Eclipse 80i microscope equipped with a CCD camera and the Spot software package. To determine semiquantitative PAC1 immunofluorescence intensity ImageJ 1.440 software was used. *Mouse colitis model and human IBD samples:* policlonal first antibodies: mouse anti-CD68 (KP1): ab125212 (Abcam), 1:300; mouse and human TRPA1 antibody: ab68847 1:300 hígításban, specificity tested by preadsorption with the immunizing peptide (ab150297, 1:100, Abcam); mouse TRPV1 antibody (ab74813, 1:300), specificity was tested by preadsorption with the immunizing peptide (ab190844, 1:100, Abcam); humán TRPV1 antibody: GP14100, 1:100, specificity tested by preadsorption with the immunizing peptide (P14100, 1:10). Secondary antibody: respective anti-rabbit or anti-guinea pig antibodies conjugated with horseradish-peroxidase (Dako-Cytomation). Development: diaminobenzidine (DAB), nuclei staining: hematoxilin.

Radioimmunassay

PACAP-38-like (PACAP-38-LI) immunoreactivity was determined with a specific and sensitive RIA method [77]. Excised skin samples were weighed and homogenized in sterile phosphate buffer solution (PBS). The tracers were mono-^{125}I-labelled peptides prepared in our laboratory. After 48-72 h incubation at 4 °C, the antibody-bound peptide was separated from the free one by addition of 100 μl separating solution. Following centrifugation the tubes were gently decanted and the radioactivity of the precipitates was measured in a gamma counter (Gamma, type: NZ310). PACAP-38 concentrations of the unknown samples were read from a calibration curve.

Luminex RNA assay

QuantiGene 2.0 Plex Assay (Plex Set 21491 MOUSE 8 plex Magnetic Beads; cat. no. 321491; Affymetrix Inc./Panomics, USA) was used to quantify directly the mRNA levels of 1 reference gene (beta-actin) and 7 target genes (Trpv1, Trpa1, Sstr1, Sstr4, Adcyap1r1, Vipr1, Vipr2) in total RNA isolated from murine distal colon samples according to the manufacturer's instructions.

Luminex Multiplex Immunassay

Distal colon samples were excised and stored in -80°C, then thawed before the assay. Samples were weighed and protease inhibitor was added (10 mg/ml phenylmethylsulfonyl fluoride: PMSF) to the PBS solution that samples were homogenized in. Then Triton X-100 was added and samples were centrifuged to eliminate cell debris. The assay contained microbead-conjugated specific antibodies for the following analytes: 1. interleukin-1β (IL-1β); 2. *monocyte chemotactic protein-1* (MCP-1 or chemokine /C-C motif/ ligand 2: CLC2); 3. *monokine induced by gamma interferon* (MIG or chemokine, C-X-C motif ligand 9: CXCL9); 4. *regulated on activation, normal T cell expressed and secreted* (RANTES or chemokine /C-C motif/ ligand 5: CCL5).

Statistics

Results were expressed as mean ± SEM. Non-parametric statistical probes were applied based on the low number of samples per group (n=3-6 animal/group): Kruskal-Wallis and Mann-Whitney test). DSS colitis Disease Activity Index: when comparing the two genotypes, two-way ANOVA with Bonferroni *post hoc* test was applied based on the higher number of samples per group (n=14/genotype) after testing normal distribution (Kolmogorov-Smirnov test). Data from skin inflammation experiments (oedema formation, PAC1 immunoreactivity): ANOVA and Bonferroni post hoc test. GraphPad Prism 5.02 for Windows software was used to perform statistical analysis. $p<0,05$ was accepted as significant.

RESULTS AND CONCLUSIONS

1. The effect of chemical and surgical denervation on the expression of non-neuronal TRPV1 in rat buccal mucosa and skin

a. Trpv1 receptor mRNA was detected with qPCR in dorsal and plantar paw skin, and buccal mucosa.

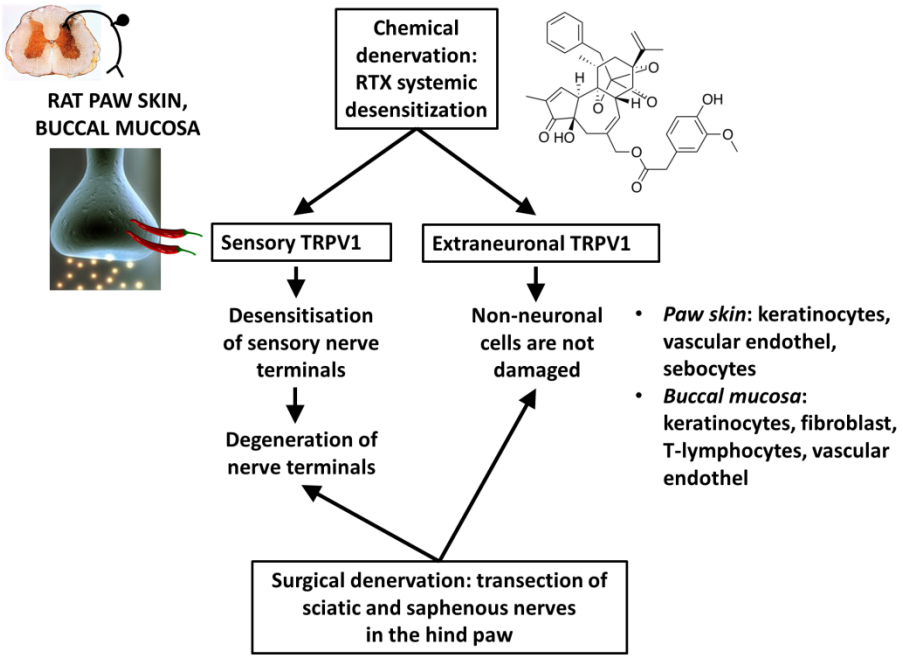
b. Relative Trpv1 mRNA expression was not altered by either chemical (RTX) desensitization, nor surgical denervation in the dorsal and ventral paw skin.

c. Buccal mucosa demonstrated the highest level of Trpv1 gene expression among tissue types followed by dorsal and plantar samples.

d. TRPV1 protein immunostaining was detected on paw skin keratinocytes, endothelial cells of capillaries in the ventral paw skin, sebocytes in the dorsal paw skin, keratinocytes in the buccal mucosa, fibroblasts, lymphocytes and vascular endothelial cells in the connective tissue.

e. The intensity of TRPV1 immunostaining did not differ between the three tissue regions and was not altered by RTX desensitization or surgical denervation.

According to our data, RTX pretreatment is cytotoxic only to capsaicin-sensitive neurons and does not damage extraneuronal TRPV1 receptors in the rat dorsal and ventral paw skin and buccal mucosa. The lack of Ca^{2+}-toxicity in non-neuronal cells can be explained by lower TRPV1 density in the outer cell membrane, different cell structure (e. g. lipid rafts, intracellular protein complexes), different sensitivity of the ion channel. RTX/capsaicin desensitiztation can still be considered a selective pharmacological method to investigate sensory TRPV1 functions. Our data suggest that therapies based on RTX/capsaicin desensitization do not damage TRPV1 extraneuronally nor non-neuronal cells expressing the receptor.



2. The effect TRPV1-PACAP connection in capsaicin-induced skin inflammation

a. PACAP-38-like immunoreactivity was detected in homogenates of different mouse skin samples. Its concentration was similar (20 és 25 fmol/mg wet tissue) in ventral and dorsal paw skin and ear skin, while it was considerably smaller (7-8 fmol/mg) in the back skin.

b. Besides PACAP-IR the peptid was also detected at the mRNA level. Its expression levels were similar among different skin regions compared to the reference gene Gapdh.

c. The specific PACAP receptor PAC1 was also detected in the mouse skin. PAC1 (Adcyap1r1) mRNA was expressed in the mouse skin at a relatively stable level, PAC1-IR was detected in the papillary layer of the dorsal paw skin.

d. Capsaicin evoked a significant, more than 2-fold increase in the plantar paw skin 24 hours after its administration. There was no change on the contralateral, non-inflamed side. In contrast, CFA injection administered into the ventral paw did not influence the PACAP-IR.

e. PACAP (Adcyap1) mRNA expression in the inflamed ventral paw skin significantly elevated 24 hours after the capsaicin treatment, while it did not change after CFA injection. The PAC1 receptor (Adcyap1r1) mRNA was upregulated after capsaicin but not CFA administration. In the dorsal paw skin PACAP and PAC1 mRNA levels remained unchanged.

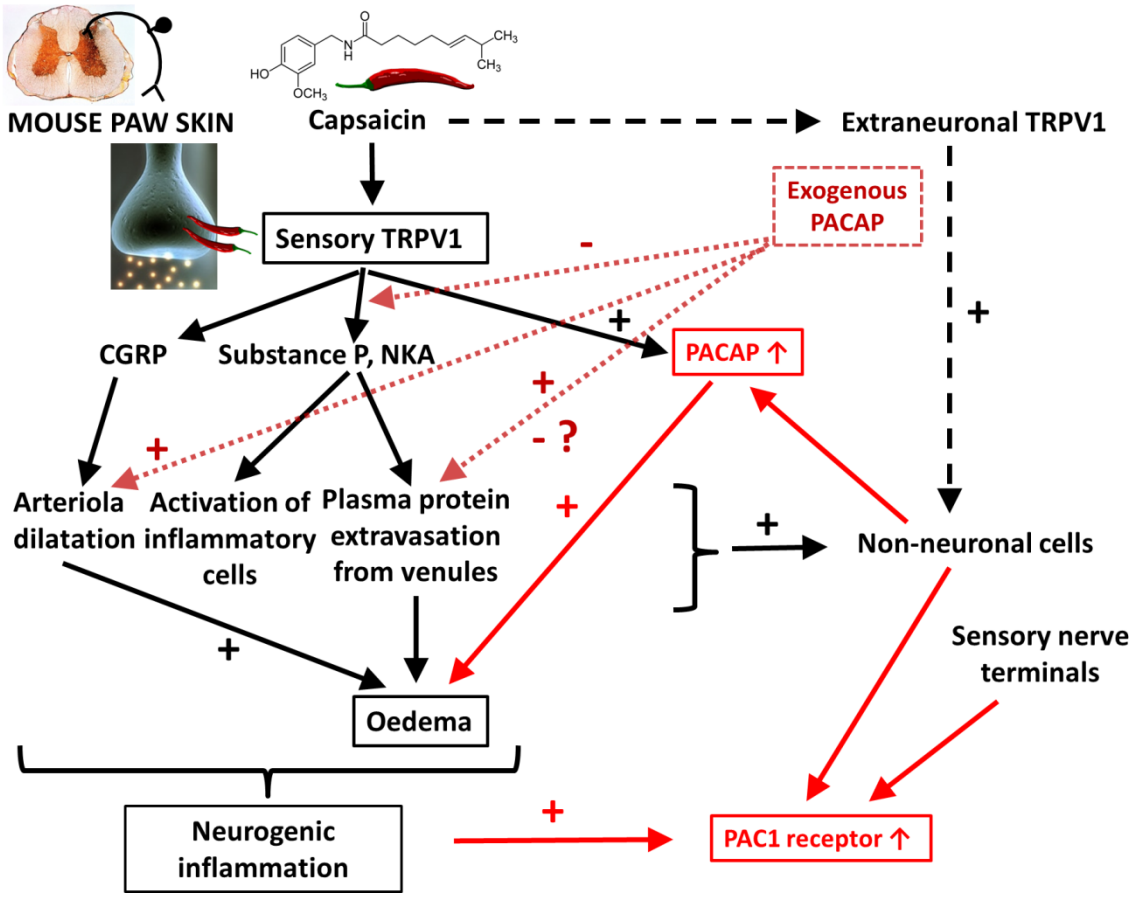
f. Capsaicin-evoked ventral paw skin oedema provoked the elevation of PAC1 receptor protein levels in WT mice based on immunohistochemical results.

g. Capsaicin-induced neurogenic inflammatory response was significantly smaller in PACAP and TRPV1 deficient animals compared to their WT counterparts.

h. Intraplantar administration of CFA resulted in oedema but without difference in PACAP (Adcyap1) and Trpv1 KO mice compared to their WT counterparts.

The expression of PACAP and its specific PAC1 receptor and their capsaicin-evoked upregulation was observed in mouse skin at the mRNA and protein levels. PACAP deficient mice demonstrated the peptide's functional relevance: PACAP has been proven to be an important mediator of TRPV1-activation-induced acute neurogenic oedema formation but

not that of CFA-induced cellular inflammation. PACAP is known to increase arteriola dilatation and plasma protein extravasation which can explain our results.



3. Expression and role of TRPA1 in colitis

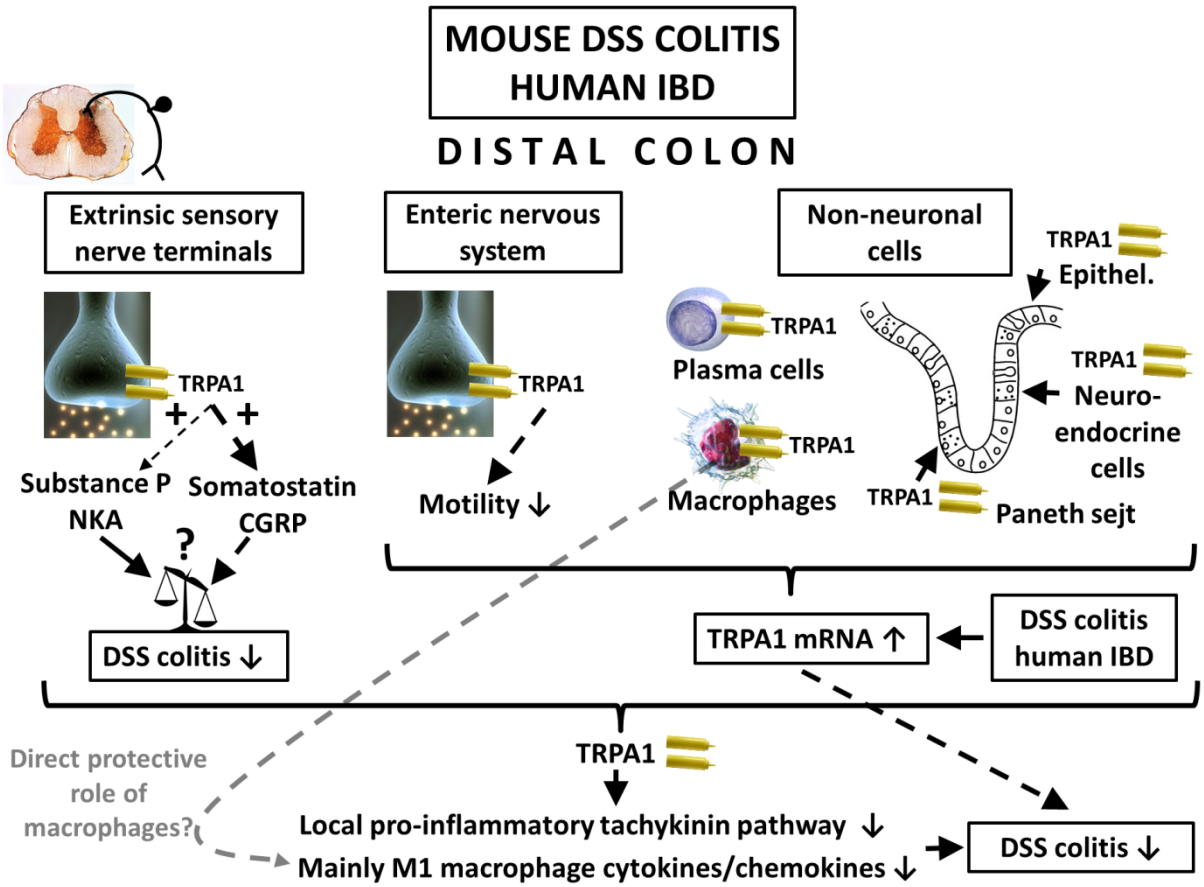
a. Various neuronal (sensory neurons and autonomous nervous system) and non-neuronal cells (intestinal epithelial cells, neuroendocrine cell, macrophages, plasma cells) express TRPA1 in mouse colitis and human inflammatory diseases.

b. TRPA1 is protective in mouse DSS-colitis based on the Disease Activity Index and histological scoring.

c. TRPA1 mRNA was upregulated in both human clinical samples (active IBD) and mouse colitis model.

d. In the presence of TRPA1 there was a significant decrease in the mRNA or protein expression levels of the local tachykinin system (substance P, NKA, NKB, NK1 receptor) and cytokine/chemokine (TNFα, IL-1β, MCP-1, MIG, BLC) levels in mouse colitis.

Activation of TRPA1 receptors in mouse DSS colitis reduced the mRNA, protein levels of the local, proinflammatry tachykinin system and several cytokines/chemokines, such as those secreted by classicaly activated M1 macrophages. Inhibition of macrophage functions may play a role by either somatostatin's effects or macrophage TRPA1. Somatostatin and CGRP released from sensory neurons may play a role in the protective effect of TRPA1. The receptor can be a promising target in the research of IBD.



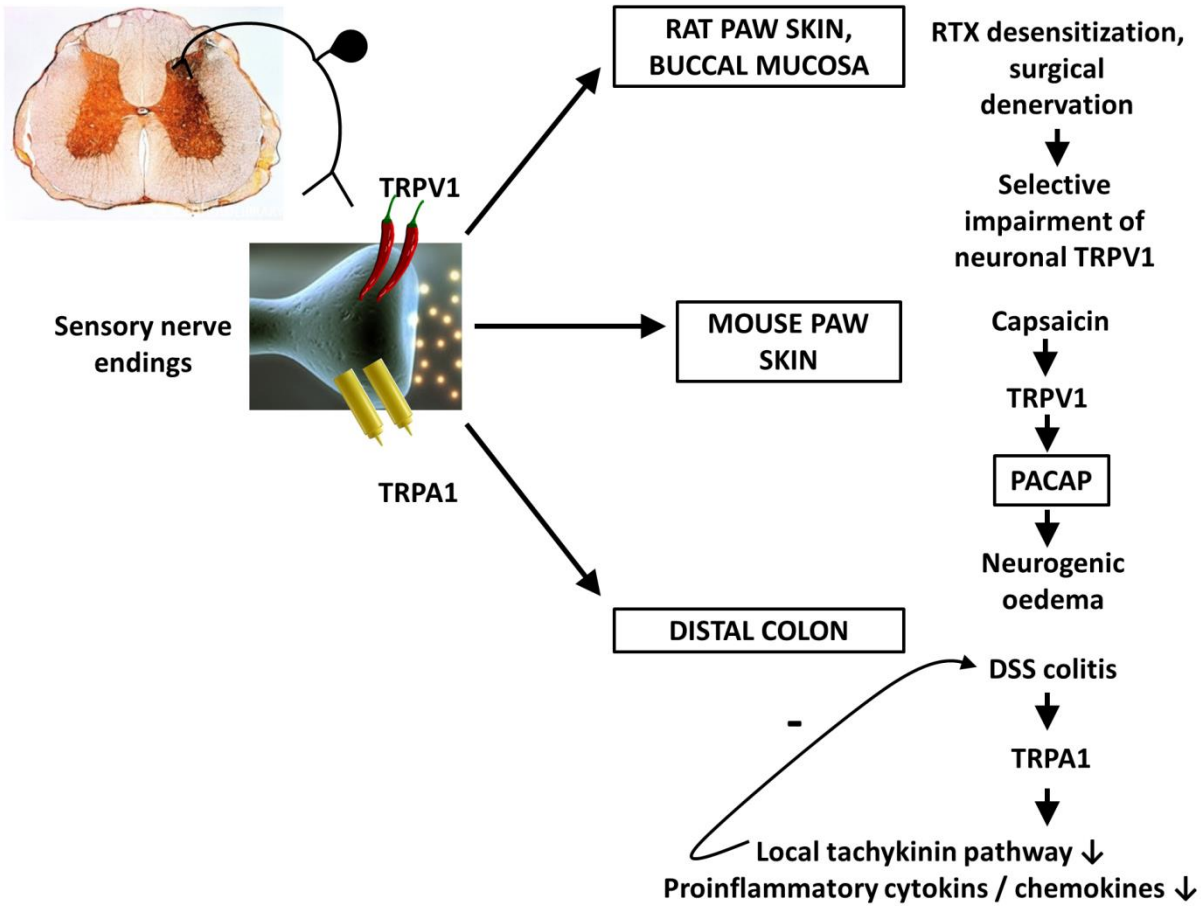
SUMMARY

The most important results of the thesis can be summarized as follows:

1) RTX pretreatment is cytotoxic only to capsaicin-sensitive neurons;

2) PACAP is an important mediator of neurogenic oedema formation induced by TRPV1 activation;

3) TRPA1 receptor is protective in the murine DSS colitis model.



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LIST OF PUBLICATIONS

Original full publications the Thesis is based upon:

Kun József, Helyes Zsuzsanna, Perkecz Anikó, Bán Ágnes, Polgár Beáta, Szolcsányi János, Pintér Erika
Effect of Surgical and Chemical Sensory Denervation on Non-neural Expression of the Transient Receptor Potential Vanilloid 1 (TRPV1) Receptors in the Rat.
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Helyes Zsuzsanna, **Kun József**, Dobrosi Nóra, Sándor Katalin, Németh József, Perkecz Anikó, Pintér Erika, Szabadfi Krisztina, Gaszner Balázs, Tékus Valéria, Szolcsányi János, *Capsaicin induces skin inflammation via Transient Receptor Potential Vanilloid-1-mediated up-regulation of Pituitary Adenylate-Cyclase Activating Polypeptide*
Submitted to the Journal of Investigative Dermatology folyóirathoz, review process is underway.
IF: 6,372

Kun József, Szitter István, Kemény Ágnes, Perkecz Anikó, Kereskai László, Pohóczky Krisztina, Vincze Áron, Gódi Szilárd, Szabó Imre, Szolcsányi János, Pintér Erika, Helyes Zsuzsanna
Upregulation of the Transient Receptor Potential Ankyrin 1 ion channel in the inflamed human and mouse colon and its protective roles
PLoS ONE, September 29th 2014; DOI: 10.1371/journal.pone.0108164
IF: 3,534

Cumulative impact factor of original publications: 6,038.

Independent citations: 4.

Other publications

Szitter István, Pintér Erika, Perkecz Anikó, Kemény Ágnes, **Kun József**, Kereskai László, Claudio Pietra, John P. Quinn, Andreas Zimmer, Alexandra Berger, Christopher J. Paige, Helyes Zsuzsanna
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IF: 2,143

Markovics Adrienn, Kormos Viktória, Gaszner Balázs, Arvin Lashgarara, Szőke Éva, Sandor Katalin, Szabadfi Krisztina, Tuka Bernadett, Tajti János, Szolcsányi János, Pintér Erika, Hitoshi Hashimoto, **Kun József**, Reglődi Dóra, Helyes Zsuzsanna
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IF: 5,403, független idézők: 15.

Presentations

J. Kun, I. Szitter, Á. Kemény, A. Perkecz, L. Kereskai, Krisztina Pohóczky, Áron Vincze, Szilárd Gódi, Imre Szabó, János Szolcsányi, Erika Pintér, Zsuzsanna Helyes
UPREGULATION OF THE TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 RECEPTOR IN THE INFLAMED HUMAN AND MOUSE COLON
The 8th International Symposium on Cell/Tissue Injury and Cytoprotection/ Organoprotection and IUPHAR Meeting of the 17th World Congress of Basic and Clinical Pharmacology, Budapest, 2014. szeptember 24-26. (*poszter*)

J. Kun, I. Szitter, Á. Kemény, A. Perkecz, L. Kereskai, Krisztina Pohóczky, Áron Vincze, Szilárd Gódi, Imre Szabó, János Szolcsányi, Erika Pintér, Zsuzsanna Helyes
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J. Kun, Zs. Helyes, I. Szitter, Á. Kemény, É. Szőke, É. Sághy, D. Ernszt, T. Bagoly, A. Perkecz, K. Pohóczky, A. Markovics, V. Tékus, E. Pintér
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J. Kun, Zs. Helyes, I. Szitter, Á. Kemény, D. Ernszt, É. Szőke, É. Sághy, T. Kovács, A. Bognár, K. Pohóczky, T. Bagoly, A. Markovics, A. Perkecz, Z. Sándor, E. Pintér
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TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 (TRPA1) RECEPTOR KNOCKOUT MICE ARE MORE SUSCEPTIBLE TO DEXTRANE-SULFATE INDUCED COLITIS
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Zs. Helyes, **J. Kun**, N. Dobrosi, K. Sandor, J. Nemeth, A. Perkecz A, E. Pinter, K. Szabadfi, V. Tekus, J. Szolcsanyi, A. Baba, D. Reglodi, T. Biro
CAPSAICIN INDUCES SKIN INFLAMMATION VIA TRPV1- MEDIATED UP-REGULATION OF PACAP
The 11th International Symposium on VIP, PACAP and Related Peptides. Konferencia helye, ideje: Pécs, Magyarország, 2013.08.27-2013.08.31. Pécs. (*előadás*)

J. Kun, Zs. Helyes, I. Szitter, Sz. Gódi, I. Szabó, Á. Kemény, K. Pohóczky, A. Perkecz, E. Pintér
A tranziens receptor potenciál ankyrin 1 (TRPA1) és vanilloid 1 (TRPV1) receptor mRNS expresszió gyulladásos bélbetegségben (IBD) és dextrán-szulfát (DSS) által indukált egér colitis modellben
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J. Kun, Zs. Helyes, I. Szitter, Sz. Gódi, I. Szabó, Á. Kemény, K. Pohóczky, A. Perkecz, E. Pintér
TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 (TRPA1) AND VANILLOID 1 (TRPV1) RECEPTOR mRNA EXPRESSION IN INFLAMMATORY BOWEL DISEASE (IBD) AND DEXTRAN SULFATE-INDUCED COLITIS IN MICE
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J. Kun, E. Pintér, I. Szitter, I. Szabó, Sz. Gódi, A. Perkecz, Zs. Helyes
A TRANZIENS RECEPTOR POTENCIÁL ANKYRIN 1 (TRPA1) RECEPTOR EXPRESSZIÓVÁLTOZÁSA GYULLADÁSOS BÉLBETEGSÉGBEN (IBD) ÉS DEXTRÁN-SZULFÁT ÁLTAL INDUKÁLT EGÉR COLITIS MODELLBEN
Magyar Anatómus Társaság, a Magyar Biofizikai Társaság, a Magyar Élettani Társaság, és a Magyar Mikrocirkulációs és Vaszkuláris Biológiai Társaság Vándorgyűlése, Debrecen, 2012. június 10-13. (*poszter*)

J. Kun, Zs. Helyes, A. Perkecz, Sz. Gódi, I. Szabó, E. Pinter
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Kisfaludy Lajos Alapítvány előadóülés, Richter Gedeon Vegyészeti Gyár Rt., Budapest, 2013. április 15. (*előadás*)

J. Kun, Zs. Helyes, A. Perkecz, Sz. Gódi, I. Szabó, E. Pinter
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6th European Congress of Pharmacology (EPHAR), Granada, Spanyolország, 2012. július 17-20. (*poszter*)

J. Kun, Zs. Helyes, A. Perkecz, Á. Bán, B. Polgár, J. Szolcsányi, E. Pintér
EFFECT OF SURGICAL AND CHEMICAL SENSORY DENERVATION ON NON-NEURAL EXPRESSION OF THE TRANSIENT RECEPTOR POTENTIAL VANILLOID 1 (TRPV1) RECEPTORS IN THE RAT
International Brain Research Organization IBRO 2012 Workshop, 2012. január 19-21, Szeged (*poszter*)

J. Kun, E. Pintér, A. Perkecz, J. Szolcsányi: "EFFECT OF SURGICAL AND CHEMICAL SENSORY DENERVATION ON NON-NEURAL EXPRESSION OF THE TRANSIENT RECEPTOR POTENTIAL VANILLOID 1 (TRPV1) RECEPTORS IN THE RAT"
The 8th International Medical Postgraduate Conference, Károly Egyetem Orvostudományi Kar, Hradec Kralove, Cseh Köztársaság, 2011. november 10-12. (*előadás*)

Other conference presentations

E. Tóth, **J. Kun**, A. Perkecz, Z. Piski, I. Gerlinger, J. Szolcsányi, E. Pintér
Nem-neurális tranziens receptor potenciál VANILLOID 1 (TRPV1) - azaz kapszaicin receptor - és ANKYRIN 1 (TRPA1) receptorok jelenléte orrpolipózisban, asztmás betegcsoporton
A MAGYAR FÜL-, ORR-, GÉGE ÉS FEJ-, NYAKSEBÉSZ ORVOSOK EGYESÜLETE 43. KONGRESSZUSA, TAPOLCA, 2014. OKTÓBER 15-18. (*előadás*)

A. Kemeny, Zs. Hajna, I. Szitter, **J. Kun**, E. Pinter, Zs. Helyes
Role of TRPV1 and TRPA1 ion channels in cigarette smoke-induced chronic airway inflammation model of the mouse
20th International Symposium on Regulatory Peptides (REGPEP2014), Kiotó, Japán, 2014. szeptember 7-10. (*poszter*)

K. Pohóczky, **J. Kun**, B. Szalontai, K. Kovács, J. Garai, A. Garami, A. Perkecz, Zs. Helyes
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20th International Symposium on Regulatory Peptides (REGPEP2014), Kiotó, Japán, 2014. szeptember 7-10. (*poszter*)

J. Kun, D. Feller, I. Szitter, Zs. Hajna, Á. Kemény, A. Perkecz, V. Csöngei, D. Ernszt, T. Kovács, J. E. Pongrácz, Zs. Helyes
CIGARETTE SMOKE-INDUCED UPREGULATION OF THE TRANSIENT RECEPTOR POTENTIAL ANKYRIN 1 ION CHANNEL IN THE MOUSE LUNG AND IN A HUMAN PULMONARY TISSUE 3-DIMENSIONAL MODEL
20th International Symposium on Regulatory Peptides (REGPEP2014), Kiotó, Japán, 2014. szeptember 7-10. (*poszter*)

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Joint Meeting of the Federation of European Physiological Societies (FEPS) and the Hungarian Physiological Society, Budapest, 2014. August 27-30. (*poszter*)

E. Toth, **J. Kun**, A. Perkecz, T. Tornoczky, I. Gerlinger, J. Szolcsanyi, E. Pinter
EXPRESSION OF TRANSIENT RECEPTOR POTENTIAL VANILLOID 1 (TRPV1) AND ANKYRIN 1 (TRPA1) RECEPTORS IN CHRONIC RHINOSINUSITIS
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K. Pohóczky, **J. Kun**, J. Garai, A. Garami, A. Perkecz, Zs. Helyes
Expression and hormone-mediated upregulation of Transient Receptor Potential Vanilloid 1 (TRPV1) and Macrophage Migration Inhibitory Factor (MIF) in the rat endometrium
Horvát Élettani Társaság Konferenciája – Élettani Társaságok 1. Regionális Konferenciája, 2013. szeptember 13-15., Fiume, Horvátország (*poszter*)

A. Markovics, V. Kormos, B. Gaszner, A. Lashgarara, E. Szoke, K. Sandor, K. Szabadfi, B. Tuka, J. Tajti, J. Szolcsanyi, E. Pinter, H. Hashimoto, **J. Kun**, D. Reglodi, Zs. Helyes
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