

CAPSAICIN AND GUT MOTILITY

SHUCHITA SINGH AND MALOY B. MANDAL*

Department of Physiology Institute of Medical Science Banaras Hindu University, Varanasi- 221005

ABSTRACT

Capsaicin is one of the most important capsaicinoids and forms the main pungent ingredient of chili peppers. It is known to release biologically active substances which affect motility of gut in different species. In human, capsaicin has been shown to alter gastric emptying time and capsaicin receptors have been implicated in irritable bowel syndrome (IBS). Capsaicin, acts through capsaicin receptor, Transient receptor potential subtype 1 (TRPV1). Capsaicin receptor immunoreactivity has been also reported in different parts of the gut in different mammalian species. Studies indicated that capsaicin mediate its effect by releasing endogenous substances like tachykinins, calcitonin gene related peptide (CGRP) and other substances in gut. The present review concentrates on effect of capsaicin on gut motility.

Keywords: Capsaicin, gut, motility, TRPV1.

INTRODUCTION

A chili pepper fruit produces compounds that produces spicy flavor of food and these compounds are known as capsaicinoids. Capsaicin is the primary capsaicinoid in chili pepper which is followed by dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin and homocapsaicin (Escogido-Reyes Maria de Lourdes et al, 2011). It is known to cause pain and hyperalgesia when applied topically in different part of the body and viscera (Drewes AM et al., 2003; LaMotte RH et al., 1992; Laird JMA et al., 2001; Gonzalez R et al., 1998; Rodriguez-Stanley S et al., 2000). Capsaicin is also known to affect gastric emptying time (Gonzalez R et al, 1998; Debreceni A et al., 1999) and it is implicated in IBS (Chan CLH et al., 2003; Akbar A et al., 2008; Akbar A et al., 2010). It mediates its affects through TRPV1 which was first identified and cloned in rat by Caterina MJ et al., 1997. Thus, capsaicin through TRPV1 is likely to mediate gut motility. Gut motility is altered by many types of stimuli through various pathways. Afferent fibers of various origin located in the different muscle layer of intestine are responsible for sensing any change in their inner environment. The afferents fibers thought

to act in response to change in tension, chemical and local substances (Ward SM et al., 2003) and capsaicin is likely to activate subpopulations of these afferent fibers (Walpole CS et al., 1996). There are several types of receptors identified appears to be involved in regulations of chemically induced contractions and relaxations. TRPV1 is a non selective cation channel that get activated by capsaicin, change in pH and temperature (Caterina MJ et al., 1997; Barthó L et al., 2004; Clapham, DE et al., 2003) and also causes contractions or relaxation of gut smooth muscle (Bartho' L et al., 2000; DE Man JG et al., 2008; Maggi CA et al., 1996; Maggi CA et al., 1986a; Maggi CA et al., 1986 b; Maggi CA et al., 1990a; Maggi CA et al., 1990b). Further, it is proposed that a member of extrinsic primary afferents represent the population of capsaicin-sensitive neurons (Holzer P, 2004).

Capsaicin: Structure and Receptor

Approximately 90% of capsaicinoids are capsaicin and dihydrocapsaicin in chili pepper fruit and these are the two most effective capsaicinoids and they differ only in the saturation of the acyl group in their

molecular structures (Walpole CS et al., 1996; Bernal MA et al., 1993; Kobata K et al., 1998). Capsaicin was first crystallized in 1876 by Tresh who also named it. In 1919, Nelson and Dawson first resolved the molecular structure of capsaicin (Nelson EK and Dawson LE, 1923) (figure 1). Capsaicin is a crystalline, lipophilic, colorless and odorless alkaloid. Its molecular weight is 305.40

g/mol and molecular formula C₁₈H₂₇NO₃ with nomenclature- Trans-8-methyl-N-vanillyl-6-nonenamide. It is alcohol and lipid soluble. Capsaicin shows *cis/trans* isomerism because the double bond of the capsaicin prevents internal rotation. Capsaicin is always occurring in the form of trans isomer because *cis* isomer form is less stable (Escrido-Reyes Maria de Lourdes et al, 2011).

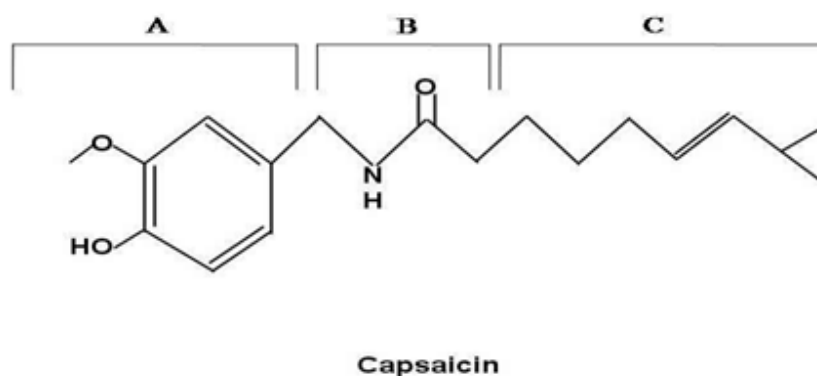


Figure 1
Structure of Capsaicin

According to structure-activity relationships, capsaicin molecule has been divided into three regions which contain- A (aromatic ring), B (amide bond) and C (hydrophobic side chain). Positions 3 and 4 of the A-ring are vital for effective agonist activity in capsaicin as well as in capsaicin analogue. The phenolic 4-OH group is of particular importance because H-bond donor/acceptor properties of the phenol group are important key for agonist activity. Further, C region required for high potency (Walpole CS et al., 1996; Katritzky AR et al., 2003). According to Barbero et al., 2010 the lateral chain length determines the bioactivity of capsaicinoids and highest activity was reported with 8 and 9 carbons atoms chain (Barbero GF et al., 2010). Capsaicin, elicits a burning sensation by activating specific (vanilloid) receptors on sensory nerve endings termed nociceptors. Capsaicin sensitive nerves are primary sensory neurons in dorsal root ganglia, nociceptive trigeminal ganglion neurons and vagal nerves originating in the nodose ganglia (Kress M and Zeilhofer HU, 1999). The capsaicin receptor was cloned and termed as vanilloid receptor subtype 1 or transient receptor potential vanilloid subtype 1 (VR1 or TRPV1). TRPV1 is structurally related to a member of the

TRP channel family and it is a non selective cation channel with six transmembrane domains and a short, pore-forming hydrophobic stretch between the fifth and sixth TM domains (Caterina MJ et al., 1997; Gunthorpe MJ et al., 2002). TRPV1 has a long amino terminus containing three ankyrin-repeat domains and a carboxyl terminus containing a TRP domain close to the sixth TM (Tominaga M and Tominaga T, 2005). The ankyrin repeats consist of a ~33-residue motif named after the cytoskeletal protein ankyrin, which contains 24 copies of these repeats and these ankyrin repeats are known to bind to many cytosolic proteins (Sedgwick SG and Smerdon SJ, 1999). According to various studies expressions of capsaicin receptor, TRPV1s are found in both sensory neurons and non-neuronal tissues (Anavi-Goffer S and Coutts AA, 2003; Matsumoto KE et al., 2009; Poli-Neto OB et al., 2009; Sim JH et al., 2001; Kullmann FA et al., 2009; Yamada T et al., 2009; Spencer NJ et al., 2008) but TRPV1 expression is mostly reported in extrinsic sensory neurons in both dorsal root ganglia and nodose ganglia. In addition, their expression was also reported in enteric neurons and extra-neuronal structures (Ichikawa H and Sugimoto T, 2003).

Capsaicin and its expression in gut

In gut, the capsaicin receptor expressions are studied and according to studies by Patterson et al., 2003; Ward et al., 2003, TRPV1 receptors in the gut are shown to be located predominantly on extrinsic afferents neurons of gut. Expressions of these TRPV1 receptors were observed in mucosa, enteric nerve plexus and musculature (Ward SM et al., 2003; Patterson LM et al., 2003). In the immunohistochemical study in mouse jejunum, colon and rectum, TRPV1 immunoreactivity was found in the mucosa, submucosal, and muscle layers and myenteric plexus. The density of TRPV1-immunoreactive axons in the rectum and distal colon was found to be much higher than those in the transverse and proximal colon (Matsumoto KE et al., 2009; Tan LL et al., 2008). It was reported that TRPV1-immunoreactivity increases in the gut of patients suffering from rectal hypersensitivity or inflammatory bowel disease (Chan CLH et al., 2003; Akbar A et al., 2008; Akbar A et al., 2010; Yiangou Y et al., 2001). Vagal and spinal afferents supplying to the gastrointestinal tract can be activated by capsaicin and this can be used as a tool to probe the role of extrinsic afferents in the control of reflex gut function (Su X et al., 1999; Blackshaw LA et al., 2000). Further, capsaicin was found to induce both contractions and relaxation of gut smooth muscle in different conditions. The contractile action of capsaicin on gut motility could be either through activation of intrinsic enteric nerves or through tachykinin released from sensory nerve endings (Bartho' L et al., 2000; DE Man JG et al., 2008). On the other hand, capsaicin induced relaxation of gut smooth muscle cells may involve calcitonin gene related peptide, vasoactive intestinal polypeptide or non-adrenergic non- cholinergic neurons (Maggi CA et al., 1996; Maggi CA et al., 1986a; Maggi CA et al., 1986 b; Maggi CA et al., 1990a; Maggi CA et al., 1990b).

Effect of capsaicin on gut motility

The action of capsaicin on gut smooth muscle is not consistent. There may be biphasic response showing both contraction and relaxation after treatment with capsaicin, in different species. Some of the studies indicated relaxation after initial contraction with a tachyphylactic effect as described in further review. In earlier study it has been reported that capsaicin induces the contractions in guinea pig isolated ileum

(Toh CC et al., 1955). Later on it was observed that contraction induced by capsaicin in guinea pig isolated ileum was followed by irreversible tachyphylaxis and capsaicin action was inhibited by hyoscine and morphine. The study also suggested that, contractile action of capsaicin may be cholinergically mediated involving extrinsic nerves (Bartho' L and Szolcsa'nyi J, 1978). In rabbit ileum capsaicin caused a concentration dependent motor response (correspond to percentage of maximum contraction produced by acetylcholine) and effect of capsaicin was reduced by hyoscine and tetrodotoxins. Such tachyphylactic response was obtained at high concentration of capsaicin (Bartho' L and Szolcsa'nyi J, 1980). A similar result was also obtained in guinea-pig taenia caeci in which capsaicin produced contraction in taenia caeci which was followed by long lasting tachyphylaxis suggesting that capsaicin-sensitive nerves excite cholinergic neurons of the myenteric plexus (Szolcsa'nyi J and Bartho' L, 1979). Further, in guinea-pig ileum, capsaicin produced a large contractile response which displayed marked tachyphylaxis. The response was reduced by atropine and substance P-autodesensitization. It was also observed that the response was completely abolished after combination of these treatments. Therefore, it was concluded that capsaicin released substance P from neurons in the ileum and in turn substance P stimulated cholinergic neurons to release acetylcholine, which induced contractions in guinea-pig ileum (Chahl LA, 1982). In another study with the guinea ileum it was suggested that contractile action of capsaicin involved interaction of neuronal NK₁ and NK₃ receptors by exciting the myenteric neurons through tachykinins released from primary afferents. The possibility of a non-tachykininergic component of the capsaicin-induced contraction could not be ruled out, because capsaicin evoked contraction was not blocked by individual component but could be blocked by combined action of NK₁ and NK₃ receptors antagonists (Bartho' L et al, 1999). In another study by Bartho et al., 2000, it was observed that P₂ purinoceptor antagonist in presence of NK₁ and NK₃ receptors antagonists reduced contractile response of capsaicin in guinea-pig ileum. Therefore, it was concluded that P₂ purinoceptor (may be ATP) caused non tachykininergic activation of cholinergic neurons in the course of the capsaicin-induced

contraction (Bartho' L et al., 2000). Further, in mouse, capsaicin was observed to produce dose dependent contractions in jejunal muscle strips which showed rapid tachyphylaxis (DE Man JG et al., 2008). Contractions induced by capsaicin were unaffected by tetrodotoxin, hexamethonium, atropine or L-NOARG but blocked by TRPV1 antagonists. However, capsaicin did not affect contractions elicited by electrical stimulation of enteric motor nerves and carbachol. Further, combination of tachykinin receptor antagonists NK₁ (RP67580), NK₂ (nepadutant) and NK₃ (SR-142801) respectively significantly reduced contractions to capsaicin. This suggested that, in the mouse intestine, capsaicin induced contractions are mediated through activation of TRPV1 by tachykinins unlike observed in guinea-pig ileum (Bartho' L et al., 2000; DE Man JG et al., 2008). Similarly, capsaicin induced transient contraction from the proximal colon to the rectum was seen to be moderately inhibited by an NK1 or NK2 receptor antagonist. The capsaicin-induced long-lasting contraction in the rectum and distal colon was also found to be markedly inhibited by an NK2 antagonist, but not by an NK1 antagonist. It was also proposed that TRPV1 channels located on the rectum and distal colon play an important role in the motor function in the large intestine (Matsumoto KE et al., 2009). Matsumoto et al., 2011 also reported that rectum of mouse was more responsive to capsaicin than other parts of the colon and effect of capsaicin was blocked by BCTC N-(4-tertiary butylphenyl)-4-(3-chloropyridin-2-yl) tetrahydropyrazine-1(2H)-carbox-amide (Matsumoto K et al., 2011).

Capsaicin is also known to relax gut smooth muscle when a selective concentration of capsaicin is used. For example a study, in guinea pig colon, transient relaxation in mucosa free circular muscle of proximal colon was seen after capsaicin application and this effect of capsaicin was partially inhibited by human alpha calcitonin gene related peptide receptor antagonist, (CGRP 8-37). It was suggested that relaxant response of capsaicin is mediated by endogenous CGRP through activation of capsaicin-sensitive primary afferent nerves (Maggi CA et al, 1996). In case of rats, it was reported that capsaicin causes relaxation of longitudinal muscle of rat duodenum and this relaxation was significantly inhibited by

tetrodotoxins suggesting the role of non-adrenergic non- cholinergic neurons (NANC). Capsaicin induced relaxation was also reduced in the presence of ATP and CGRP. It was proposed that capsaicin caused release of CGRP and released CGRP might produce NANC relaxation both by directly and by releasing the endogenous NANC neurotransmitters (Maggi CA et al., 1986a; Maggi CA et al., 1986 b). In the rat colon, capsaicin and hCGRP8-37 have been reported to inhibit the peristaltic response due to muscle stretch or mucosal stimulation (Grider JR, 1994). Similar response was also seen in rat ileum (Allescher HD, 1992; Wali FA, 1985). In longitudinal and circular muscle of human jejunum and ileum capsaicin induced complex motor response has been reported. In circular muscle of human small intestine; capsaicin produced relaxation and decreased spontaneous activity. Capsaicin was shown to evoke a tetrodotoxin-resistant release of VIP (vasoactive intestinal polypeptide) in these experiments. It was speculated that after capsaicin treatment VIP is released from sensory nerves of the human gut and produce the motor response (Maggi CA et al., 1990a). In a study with human taenia coli, it was observed that capsaicin produced relaxation and the effect could be blocked by anti-vasoactive intestinal polypeptide serum (Maggi CA et al., 1990b). Capsaicin also found to induce relaxation of mucosa-free circular strips of the human sigmoid colon *in vitro* and could be reduced by the nitric oxide synthase inhibitor NG-nitro-L-arginine (L-NOARG) or by the guanylate cyclase inhibitor 1*H*-[1,2,4]oxadiazolo[4,3- a]quinoxalin-1-one (Bartho' L et al., 2002). The relaxant effect of capsaicin in other species was also reported. For example, capsaicin, 1 μ M in mouse colon, 2 μ M in guinea-pig and 0.3 μ M in human ileum and appendix were seen to produce relaxation of gut muscle. Response of capsaicin was inhibited by the L-NOARG in most of the studies except in circular muscle of the guinea-pig colon. However, tetrodotoxin reduced inhibitory effect of capsaicin in the mouse colon but failed to significantly reduce the inhibitory effect of capsaicin in guinea-pig colon, human ileum and appendix (Benko Rita et al., 2005).

Capsaicin was also seen to produce biphasic effect i.e. inhibitory as well as excitatory effect on gut of different species. Studies in guinea-pig ileum by Maggi et al., 1988, Bartho et al., 1987 and Bartho

et al., 1991, it was reported that capsaicin produced both excitatory as well as inhibitory action on the longitudinal muscle of the ileum. This effect was insensitive to tetrodotoxins and there is a good evidence for the involvement of CGRP in the relaxation effect (Maggi CA et al., 1988; Bartho' L et al., 1987; Bartho' L et al., 1991). In guinea pig distal colon, capsaicin inhibited spontaneous contractions and this response was reduced by tetrodotoxins. Thus, it suggested the involvement of non adrenergic, non cholinergic (NANC) mechanisms (Maggi CA et al., 1987). In other study on guinea-pig isolated ileum capsaicin produced variable responses. For example, it produced an initial short-lasting stimulation of peristalsis followed by a prolonged inhibition of peristaltic activity and a high concentration of capsaicin (33 μ M) completely abolished peristalsis which was fully reversible on removal. These excitatory/Inhibitory effects of capsaicin were inhibited by the combination of both NK1 and NK2 receptor antagonists and nitric oxide synthase inhibitor and CGRP antagonist (Bartho' L and Holzer P, 1995). In the experiment on rabbit colon capsaicin was observed to produce a concentration-dependent transient response of longitudinal muscle contractions, followed by prolonged inhibition of spontaneous contraction (Mayer EA et al., 1990). The initial response was blocked by the substance P

antagonist spantide and by atropine. The inhibitory effect was reduced by repeated exposure of muscle to CGRP. It was concluded that tachykinins and CGRP appeared to be involved in the excitatory and inhibitory effects of capsaicin, respectively (Mayer EA et al., 1990).

Thus, it appears that capsaicin has various types of effect on the gut smooth muscle which varies from species to species and from segment to segment of gut and the detailed mechanisms remains to be worked out.

CONCLUSION

The effect of capsaicin in gut motility is complex and the mechanism of action of capsaicin is yet to be adequately explained. Nevertheless, capsaicin has definitive effect on gut motility. Further, research on capsaicin receptors and its mediators may help in understanding pathophysiology of various gut motility related disorders including IBS, to resolve the various issues pertaining to their clinical management.

ACKNOWLEDGEMENT

University grant commission (New Delhi) for financial assistant.

REFERENCES

1. Akbar A , Yiangou Y , Facer P, Walters J R F , Anand P , Ghosh S. Increased capsaicin receptor TRPV1-expressing sensory fibres in irritable bowel syndrome and their correlation with abdominal pain. *Gut* 2008; 57: 923-929.
2. Akbar A, Yiangou Y, Facer P, Brydon WG, Walters JR, Anand P et al. Expression of the TRPV1 receptor differs in quiescent inflammatory bowel disease with or without abdominal pain. *Gut* 2010; 59 :767-74.
3. Allescher HD, Sattler D, Piller C Schusdziarra, V Classen, M. Ascending neural pathways in the rat ileum in in vitro-effect of capsaicin and involvement of nitric oxide. *Eur. J. Pharmacol.* 1992; 217: 153-162.
4. Anavi-Goffer S, Coutts AA. Cellular distribution of vanilloid VR1 receptor immunoreactivity in the guinea-pig myenteric plexus. *Eur J Pharmacol.* 2003; 458: 61 – 71.
5. Barbero GF, Molinillo JMG, Varela RM, Palma M, Macias FA and Barroso CG. Application of Hansch's model to capsaicinoids and capsinoids: a study using the quantitative structure-activity relationship. A novel method for the synthesis of capsinoids. *J. Agric. Food Chem.* 2010; 58: 3342-3349.
6. Barthó L, Benkó R, Patacchini R, Pethő G, Holzerpetsche U, Holzer P, et al. Effects of capsaicin on visceralsmooth muscle: a valuable tool for sensory neurotransmitter identification. *Eur J Pharmacol.* 2004; 500: 143-157.
7. Bartho' L, Benko' R, La'za'r Zs, Ille'nyi L, Horva'th O' P. Nitric oxide is involved in the relaxant effect of capsaicin in the human

- sigmoid colon circular muscle. Naunyn-Schmiedeberg's Arch. Pharmacol. 2002; 366: 496–500.
8. Barthó L, Holzer P. The inhibitory modulation of guinea-pig intestinal peristalsis caused by capsaicin involves calcitonin gene-related peptide and nitric oxide. Naunyn-Schmiedeberg's Arch. Pharmacol. 1995; 353: 102–109.
 9. Barthó L, Ko'cza'n G, Holzer P, Maggi CA, Szolcsa'nyi J. Antagonism of the effects of calcitonin gene-related peptide and of capsaicin on the guinea-pig isolated ileum by human alpha-calcitonin gene-related peptide (8-37). Neurosci. Lett. 1991; 129: 156–159.
 10. Barthó L, La'za'r Zs, Le'na'rd Jr. L, Benko' R, To' th, G, Penke B, et al. Evidence for the involvement of ATP, but not of VIP/PACAP or nitric oxide, in the excitatory effect of capsaicin in the small intestine. Eur. J. Pharmacol. 2000; 392: 183–188.
 11. Barthó L, Le'na'rd Jr. L, Patacchini R, Halmai V, Wilhelm M, Holzer P, et al. Tachykinin receptors are involved in the local efferent motor response to capsaicin in the guinea-pig small intestine and oesophagus. Neuroscience. 1999; 90: 221–228.
 12. Barthó L, Petho' G, Antal A, Holzer P, Szolcsa'nyi J. Two types of relaxation due to capsaicin in the guinea-pig ileum. Neurosci. Lett. 1987; 81: 146–150.
 13. Barthó L, Szolcsa'nyi J. The mechanism of the motor response to periarterial nerve stimulation in the rabbit. Br. J. Pharmacol. 1980; 70: 193–195.
 14. Barthó L, Szolcsa'nyi J. The site of action of capsaicin on the guinea-pig isolated ileum. Naunyn-Schmiedeberg's Arch. Pharmacol. 1978; 305:75–81.
 15. Benko Rita, Lazar Zsofia, Undi Sarolta, Illenyi Laszlo, Antal Andras, Horvath Ors-Peter, et al. Inhibition of nitric oxide synthesis blocks the inhibitory response to capsaicin in intestinal circular muscle preparations from different species. Life Sci. 2005; 76: 2773–2782.
 16. Bernal MA, Calderon AA, Pedreno MA, Muñoz R, Ros Barceló A and Merino de Caceres F. Capsaicin oxidation by peroxidase from *Capsicum annuum* (variety Annum) fruits. J. Agric. Food Chem. 1993; 41: 1041–1044.
 17. Blackshaw LA, Page AJ, Partosoedarso ER. Acute effects of capsaicin on gastrointestinal vagal afferents. Neuroscience. 2000; 96: 407 – 416.
 18. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD and Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997; 389:816–824.
 19. Chahl LA. Evidence that the contractile response of the guinea-pig ileum to capsaicin is due to substance P release. Naunyn-Schmiedeberg's Arch. Pharmacol. 1982; 319: 212–215.
 20. Chan CLH, Facer P, Davis JB, Smith GD, Egerton J, Bountra C, et al. Sensory fibres expressing capsaicin receptor TRPV1 in patients with rectal hypersensitivity and faecal urgency. Lancet 2003; 361: 385-391.
 21. Clapham, DE, Montell C, Schultz G, and Julius D. International Union of Pharmacology: XLIII. Compendium of voltage-gated ion channels: transient receptor potential channels. Pharmacol. Rev. 2003; 55: 591–596.
 22. DE Man JG, Boeckx S, Anguille S, DE Winter BY, DE Schepper HU, Herman AG, et al. Functional study on TRPV1-mediated signalling in the mouse small intestine: involvement of tachykinins receptors. Neurogastroenterol Motil. 2008; 20: 546–556.
 23. Debreceni A, Abdel-Salam OM, Figler M, Juricskay I, Szolcsányi J, Mózsik G. Capsaicin increases gastric emptying rate in healthy human subjects measured by ¹³C-labeled octanoic acid breath test. J Physiol Paris. 1999; 93: 455-60.
 24. Drewes AM, Schipper KP, Dimcevski G, Petersen P, Gregersen H, Funch-Jensen P et al., Gut pain and hyperalgesia induced by capsaicin: a human experimental model. Pain. 2003; 104: 333-41.
 25. Escogido-Reyes Maria de Lourdes, Mondragon-Gonzalez Edith G and Tzompantzi-Vazquez Erika. Chemical and Pharmacological Aspects of Capsaicin. Molecules 2011; 16: 1253-1270.

26. Gonzalez R, Dunkel R, Koletzko B, Schusdziaarra V, Allescher HD. Effect of capsaicin-containing red pepper sauce suspension on upper gastrointestinal motility in healthy volunteers. *Dig Dis Sci.* 1998; 43: 1165–71.
27. Grider JR. CGRP as a transmitter in the sensory pathway mediating peristaltic reflex. *Am J Physiol.* 1994; 266: G1139–G1145.
28. Gunthorpe MJ, Benham CD, Randall A, Davis JB. The diversity in the vanilloid (TRPV) receptor family of ion channels. *Trends Pharmacol Sci.* 2002; 23: 183 – 191.
29. Holzer P. TRPV1 and the gut: from a tasty receptor for a painful vanilloid to a key player in hyperalgesia. *Eur J Pharmacol.* 2004; 500: 231–241.
30. Ichikawa H, Sugimoto T. The co-expression of VR1 and VRL-1 in the rat vagal sensory ganglia. *Brain Res.* 2003; 980: 293 – 296.
31. Katritzky AR, Xu YJ, Vakulenko AV, Wilcox AL and Bley KR. Model compounds of caged capsaicin: design, synthesis, and photoreactivity. *J Org Chem.* 2003, 68, 9100–9104.
32. Kobata K, Kawamura M, Toyoshima M, Tamura Y, Ogawa S and Watanabe T. Lipase catalyzed synthesis of capsaicin analogs by amidation of vanillylamine with fatty acid derivatives. *Biotechnol Lett.* 1998; 20: 451–454.
33. Kress M, Zeilhofer HU. Capsaicin, protons and heat: new excitement about nociceptors. *Trends Pharmacol Sci.* 1999; 20:112–118.
34. Kullmann FA, Shah MA, Birder LA, de Groat WC. Functional TRP and ASIC-like channels in cultured urothelial cells from the rat. *Am J Physiol Renal Physiol.* 2009; 296(4): 892 – 901.
35. Laird JMA, Martinez-Caro L , Garcia-Nicas E and Cervero F. A new model of visceral pain and referred hyperalgesia in the mouse. *Pain.* 2001; 92: 335–342.
36. LaMotte RH, Lundberg LE , and Torebjörk HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *J Physiol.* 1992; 448: 749–764.
37. Maggi CA, Giuliani S, Santicioli P, Patacchini R, Said SI, Theodorsson E, et al. Direct evidence for the involvement of vasoactive intestinal polypeptide in the motor response of the human isolated ileum to capsaicin. *Eur J Pharmacol.* 1990a; 185: 169– 178.
38. Maggi CA, Giuliani S, Zagorodnyuk V. Calcitonin gene-related peptide (CGRP) in the circular muscle of guinea-pig colon: role as inhibitory transmitter and mechanisms of relaxation. *Regul Pept.* 1996; 61: 27– 36.
39. Maggi CA, Manzini S, Giuliani S, Santicioli P, Meli A. Extrinsic origin of the capsaicin-sensitive innervation of rat duodenum: possible involvement of calcitonin gene-related peptide (CGRP) in the capsaicin-induced activation of intramural non-adrenergic non-cholinergic neurons. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1986 b; 334: 172–180.
40. Maggi CA, Meli A, Santicioli P. Four motor effects of capsaicin on guinea-pig distal colon. *Br J Pharmacol.* 1987; 90: 651–660.
41. Maggi CA, Patacchini R, Santicioli P, Theodorsson E, Meli A. Several neuropeptides determine the visceromotor response to capsaicin in the guinea-pig isolated ileal longitudinal muscle. *Eur J Pharmacol.* 1988; 148: 43–49.
42. Maggi CA, Santicioli P, Manzini S, Meli A. Capsaicin activates neurogenic non-adrenergic non- cholinergic relaxation of the isolated rat duodenum. *Eur J Pharmacol.* 1986a; 120: 367-370.
43. Maggi CA, Theodorsson E, Santicioli P, Patacchini R, Barbanti G, Turini D, Renzi D, Giachetti A. Motor response of the human isolated colon to capsaicin and its relationship to release of vasoactive intestinal polypeptide. *Neuroscience* 1990b; 39: 833–841.
44. Matsumoto K, Hosoya T, Tashima K, Namiki T, Murayama T and Horiea S. Distribution of transient receptor potential vanilloid 1 channel-expressing nerve fibers in mouse rectal and colonic enteric nervous system: relationship to peptidergic and nitrenergic neurons. *Neuroscience.* 2011; 172: 518–534.
45. Matsumoto KE, Kurosawa E, Terui H, Hosoya T, Tashima K, Murayama T, et al. Localization of TRPV1 and contractile effect of capsaicin in mouse large intestine: High abundance and sensitivity in rectum and distal

- colon. *Am J Physiol Gastrointest Liver Physiol.* 2009; 297: 348–360.
46. Mayer EA, Koelbel CB, Snape WJ Jr, Eysselein V, Ennes H, Kodner A. Substance P and CGRP mediate motor response of rabbit colon to capsaicin. *Am J Physiol.* 1990; 259: G889–G897.
47. Nelson EK and Dawson LE. The constitution of capsaicin, the pungent principle of *Capsicum*. III. *J Am Chem Soc.* 1923; 45: 2179-2181.
48. Patterson LM, Zheng H, Ward SM, Berthoud HR. Vanilloid receptor (VR1) expression in vagal afferent neurons innervating the gastrointestinal tract. *Cell Tissue Res.* 2003; 311:277–287.
49. Poli-Neto OB, Filho AA, Rosa e Silva JC, Barbosa Hde F, Candido Dos Reis FJ. Increased capsaicin receptor TRPV1 in the peritoneum of women with chronic pelvic pain. *Clin J Pain.* 2009; 25(3): 218 – 222.
50. Rodriguez-Stanley S, Collings KL, Robinson M, Owen W, Miner Jr PB. The effects of capsaicin on reflux, gastric emptying and dyspepsia. *Aliment Pharmacol Ther.* 2000; 14: 129–34.
51. Sedgwick SG, Smerdon SJ. The ankyrin repeat: a diversity of interactions on a common structural framework. *Trends Biochem Sci* 1999; 24: 311–316.
52. Sim JH, Kim YC, Kim SJ, Lee SJ, Suh SH, Jun JY, et al. Capsaicin inhibits the voltage-operated calcium channels intracellularly in the antral circular myocytes of guinea-pig stomach. *Life Sci.* 2001; 68(21): 2347 – 2360.
53. Spencer NJ, Kerrin A, Singer CA, Hennig GW, Gerthoffer WT, Mc-Donnell O. Identification of capsaicin-sensitive rectal mechanoreceptors activated by rectal distension in mice. *Neuroscience.* 2008; 153(2):518 – 534.
54. Su X, Wachtel RE, Gebhart GF. Capsaicin sensitivity and voltage gated sodium currents in colon sensory neurons from rat dorsal root ganglia. *Am J Physiol.* 1999; 277: 1180 – 1188.
55. Szolcsa'nyi J, Bartho' L. Capsaicin-sensitive innervation of the guinea-pig taenia caeci. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1979; 309: 77– 82.
56. Tan LL, Bornstein JC, Anderson CR. Distinct chemical classes of medium-sized transient receptor potential channel vanilloid 1-immunoreactive dorsal root ganglion neurons innervate the adult mouse jejunum and colon. *Neuroscience.* 2008; 156: 334 – 343.
57. Toh CC, Lee TS, Kiang AK. The pharmacological actions of capsaicin and analogues. *Br J Pharmacol.* 1955; 10: 175–182.
58. Tominaga M, Tominaga T. Structure and function of TRPV1. *Pflugers Arch.* 2005; 451: 143-150.
59. Wali FA. Possible involvement of substance P in the contraction produced by periarterial nerve stimulation in the rat ileum. *J Auton Pharmacol.* 1985; 5: 143–148.
60. Walpole CS, Bevan S, Bloomfield G, Breckenridge R, James IF, Ritchie T, et al. Similarities and differences in the structure-activity relationships of capsaicin and resiniferatoxin analogues. *J Med Chem.* 1996; 39: 2939-2952.
61. Ward SM, Bayguinov Julia, Won Kyung-Jong, Grundy David and Berthoud Hans R. Distribution of the Vanilloid Receptor (VR1) in the Gastrointestinal Tract. *The Journal of Comparative Neurology* 2003; 465: 121–135.
62. Yamada T, Ugawa S, Ueda T, Ishida Y, Kajita K, Shimada S. Differential localizations of the transient receptor potential channels TRPV4 and TRPV1 in the mouse urinary bladder. *J Histochem Cytochem.* 2009; 57(3): 277 – 287.
63. Yiangou Y, Facer P, Dyer Nhc, Chan Clh, Knowles C, Williams Ns, Anand P. Vanilloid receptor 1 immunoreactivity in inflamed human bowel. *Lancet* 2001; 357: 1338-1339.