British Journal of Pharmacology (2009), 156, 728–729

0007-1188/09
www.brjpharmacol.org

COMMENTARY

Re-sensitization of neuropeptide receptors: should we stop the recycling?

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Neurogenic inflammation, an important component of many disease states, is mediated by the release of neuropeptides from sensory nerves. To date, it has been possible to inhibit neurogenic inflammation using neuropeptide receptor blockers or by prevention of neuropeptide release. In the current edition of the *British Journal of Pharmacology*, Cattaruzza and co-workers discuss a novel way of blocking the action of neuropeptides. They have shown that the re-sensitization of the substance P neurokinin-1 receptor and the substance P-induced pro-inflammatory effects are mediated by the enzyme, endothelin-converting enzyme 1 (ECE-1). Therein, they showed that ECE-1 inhibition could prevent the re-sensitization process. This is exciting progress in our understanding of neurogenic inflammation, but it remains to be seen how inhibition of receptor recycling via ECE-1 blockade will affect other inflammatory pathways.
British Journal of Pharmacology (2009) **156**, 728–729; doi:10.1111/j.1476-5381.2008.00101.x

Keywords: neuropeptides; neurogenic inflammation; re-sensitization; endothelin-converting enzyme 1; endothelial cells

Abbreviations: CGRP, calcitonin gene-related peptide; ECE-1, endothelin-converting enzyme 1; ET-1, endothelin-1; NK_1, neurokinin-1; TRPV1, transient receptor potential vanilloid 1

Neurogenic inflammation is defined as the oedema formation, increased blood flow and inflammatory cell recruitment observed after stimulation of sensory nerves (Aδ- and C-fibres) and release of neuropeptides, most importantly substance P and calcitonin gene-related peptide (CGRP). Substance P is a potent mediator of increased microvascular permeability through its action on post-capillary endothelial cells (Lembeck and Starke, 1963). In addition, substance P has an effect on neutrophil accumulation (Cao *et al.*, 2000). CGRP, on the other hand, mediates an increase in blood flow within the microvasculature (Brain *et al.*, 1985). The effects of these neuropeptides can essentially be blocked in one of three ways: blockade of their receptor target, prevention of their release from sensory nerves or preventing the re-sensitization of their receptors after desensitization, as shown by Cattaruzza *et al.* (2009) in this issue of the *British Journal of Pharmacology*. Cattaruzza *et al.* concentrate in particular on the re-sensitization to the inflammatory effects of substance P.

Substance P exerts its effects principally through an action on the neurokinin-1 (NK_1) receptor and this receptor has, for many years, been pursued as a potential target for inflammatory disease. However, in spite of promising pre-clinical studies, NK_1 receptor antagonists/blockers have not found a successful niche in the clinic. Interestingly, Grant *et al.* (2002) found that capsaicin-induced increases in blood flow are actually enhanced in the ears of NK_1 receptor knock-out mice compared with wild-type controls. The actions of both NK_1 and CGRP receptors are required to prevent this augmentation. This is one indication that it may be more effective to block the effects of multiple, rather than single neuropeptides.

Indeed, the blockade of all neuropeptide release from nerves has already been addressed pharmacologically by targeting the transient receptor potential vanilloid 1 (TRPV1) receptor. The TRPV1 receptor is expressed on a subset of Aδ- and C-fibres and is activated by a variety of stimuli, including capsaicin (the pungent component of hot chilli peppers), noxious heat (>43°C; Caterina *et al.*, 2000) and low pH (<6.0 at room temperature; Jordt *et al.*, 2000). This receptor has been shown to play a significant role in the pain and inflammation associated with a variety of disease states. For example, mice genetically modified to lack the TRPV1 receptor demonstrated an increased threshold to noxious heat, a reduction in pathological biomarkers (e.g. cytokines) and decreased tissue swelling in a model of murine joint inflammation (Caterina *et al.*, 2000; Keeble *et al.*, 2005). Several TRPV1 receptor antagonists have now been developed and their clinical success has been widely anticipated. Unfortunately, adverse effects in humans are hindering their progress.

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Received 23 October 2008; accepted 6 November 2008

More specifically, these drugs cause hyperthermia in humans that is even observed with drugs that do not cross the blood–brain barrier (Tamayo *et al.*, 2008).

Until recently, we have only understood how to target the neuropeptide receptors and their release, in pharmacological terms. However, in this issue of the *British Journal of Pharmacology*, Cattaruzza *et al.* present novel findings regarding the mechanisms underlying the re-sensitization of the substance P receptor and concomitant neurogenic inflammation. In summary, they found that a peptidase, unrelated to substance P, the endothelin-converting enzyme 1 (ECE-1), promotes the recycling and re-sensitization of NK_1 receptors, by degrading endocytosed substance P in endothelial cell endosomes. This intracellular degradation facilitated the re-appearance of the pro-inflammatory effects of substance P, that is, re-sensitization to substance P. Previous findings have shown that CGRP and somatostatin receptor recycling are also promoted by ECE-1 (Padilla *et al.*, 2007; Roosterman *et al.*, 2008), demonstrating that inhibition of ECE-1 can target several neuropeptides. What is particularly intriguing about the findings of Cattaruzza *et al.* is that they could indicate that pathways for re-sensitizing neuropeptide receptors differ between tissue types. For example, ECE-1 is most abundant in endothelial cells and so inhibition of ECE-1 may not affect the re-sensitization of these receptors in the spinal cord, for example. In the future, it will be very interesting to see which enzymes/pathways are responsible for re-sensitization of neuropeptide receptors in different tissues and how this will affect specific disease states.

However, the biggest potential disadvantage of ECE-1 as a therapeutic target is its lack of specificity in terms of the peptides metabolized. Of course, ECE-1 is pivotal to the production of endothelin-1 (ET-1), but it is also involved in the degradation of bradykinin and amyloid-beta peptides (Nalivaeva *et al.*, 2008). Inhibition of ET-1 production is a promising target for the treatment of cardiovascular disease in its own right, but there is concern regarding teratogenic effects (Kirkby *et al.*, 2008). Furthermore, inhibition of bradykinin accumulation could lead to enhanced oedematous effects of this important pro-inflammatory mediator (Jandeleit-Dahm, 2006). Finally, there has been a recent interest in ECE-1 as a potential target for the treatment of Alzheimer's disease based on its role in amyloid-beta peptide degradation (Nalivaeva *et al.*, 2008). Inhibition of ECE-1 could therefore deleteriously affect the progression of this degenerative disease. Thus, in conclusion, the paper by Cattaruzza *et al.* is an exciting step in our understanding of neurogenic inflammation, but there are clearly many reasons to be cautious, when considering whether we should stop the receptor recycling process altogether.

Acknowledgements

J.K. is supported by a Capacity Building Award in Integrative Mammalian Biology funded by the BBSRC, BPS, HEFCE, KTN, MRC and SFC.

References

Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I (1985). Calcitonin gene-related peptide is a potent vasodilator. *Nature* **313**: 54–56.

Cao T, Pintér E, Al-Rashed S, Gerard N, Hoult JR, Brain SD (2000). Neurokinin-1 receptor agonists are involved in mediating neutrophil accumulation in the inflamed, but not normal, cutaneous microvasculature: an in vivo study using neurokinin-1 receptor knockout mice. *J Immunol* **164**: 5424–5429.

Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR *et al.* (2000). Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* **288**: 306–313.

Cattaruzza F, Cottrell GS, Vaksman N, Bunnett NW (2009). Endothelin-converting enzyme 1 promotes re-sensitization of neurokinin 1 receptor-dependent neurogenic inflammation. *Br J Pharmacol* **156**: 730–739.

Grant AD, Gerard NP, Brain SD (2002). Evidence of a role for NK1 and CGRP receptors in mediating neurogenic vasodilatation in the mouse ear. *Br J Pharmacol* **135**: 356–362.

Jandeleit-Dahm KA (2006). Dual ACE/NEP inhibitors – more than playing the ACE card. *J Hum Hypertens* **20**: 478–481.

Jordt SE, Tominaga M, Julius D (2000). Acid potentiation of the capsaicin receptor determined by a key extracellular site. *Proc Natl Acad Sci USA* **97**: 8134–8139.

Keeble J, Russell F, Curtis B, Starr A, Pinter E, Brain SD (2005). Involvement of transient receptor potential vanilloid 1 in the vascular and hyperalgesic components of joint inflammation. *Arthritis Rheum* **52**: 3248–3256.

Kirkby NS, Hadoke PW, Bagnall AJ, Webb DJ (2008). The endothelin system as a therapeutic target in cardiovascular disease: great expectations or bleak house? *Br J Pharmacol* **153**: 1105–1119.

Lembeck F, Starke K (1963). Substance P content and effect of capillary permeability of extract of various parts of human brain. *Nature* **199**: 1295–1296.

Nalivaeva NN, Fisk LR, Belyaev ND, Turner AJ (2008). Amyloid-degrading enzymes as therapeutic targets in Alzheimer's disease. *Curr Alzheimer Res* **5**: 212–224.

Padilla BE, Cottrell GS, Roosterman D, Pikios S, Muller L, Steinhoff M *et al.* (2007). Endothelin-converting enzyme-1 regulates endosomal sorting of calcitonin receptor-like receptor and beta-arrestins. *J Cell Biol* **179**: 981–997.

Roosterman D, Kempkes C, Cottrell GS, Padilla BE, Bunnett NW, Turck CW *et al.* (2008). Endothelin-converting enzyme-1 degrades internalized somatostatin-14. *Endocrinology* **149**: 2200–2207.

Tamayo N, Liao H, Stec MM, Wang X, Chakrabarti P, Retz D *et al.* (2008). Design and synthesis of peripherally restricted transient receptor potential vanilloid 1 (TRPV1) antagonists. *J Med Chem* **51**: 2744–2757.